Hypomanic Episode During Recurrent Gastric Cancer Treatment: Report of a Rare Case and Literature Review

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S-1 plus cisplatin is the standard chemotherapy for recurrent gastric cancer. While depression and delirium are frequent in cancer patients, hypomania during chemotherapy is rare. We describe a rare case of hypomania during S-1 plus cisplatin treatment for recurrent gastric cancer. A 66-year-old woman, with no previous psychiatric disorder, received S-1 plus cisplatin for recurrent gastric cancer. She showed peculiar behavior. Physical examination, urine, blood and imaging findings were normal. There was no gastric cancer progression. During psychiatric consultation, she behaved inappropriately. However, she behaved normally while performing daily activities. She manifested a persistently elevated, expansive or irritable mood, clearly different from her usual non-depressed state, meeting hypomania diagnostic criteria. Her condition did not require chemotherapy discontinuation or additional medication. During the second and subsequent S-1 plus cisplatin cycles, symptoms were stable. Cancer patients often have adjustment disorders, depression and delirium, but rarely hypomania. Our patient showed no significant changes in blood biochemistry and brain and whole body imaging. While S-1 plus cisplatin-induced hypomania cannot be excluded, hypomanic symptoms did not improve during the chemotherapy rest period, nor was there deterioration during subsequent cycles, suggesting drug-induced mania to be unlikely. Possible onset mechanisms include manic defense phenomena, common with stressful life events. There are no reports of recurrent gastric cancer patients experiencing hypomania during S-1 or S-1 plus cisplatin therapy, i.e. our patient represents a rare course. Clinicians should recognize psychosis or mood disorders during gastric cancer treatment. Further accumulation of such rare cases might elucidate pathological mechanisms underlying hypomania in cancer patients.

Key words: hypomania – gastric cancer – S-1 plus cisplatin (CDDP)
INTRODUCTION
Gastric cancer remains among the most frequent causes of death from cancer in Japan, despite dramatic advances in diagnosis and treatment. Outcomes are poor in patients with unresectable and/or metastatic gastric cancer. In Japan, chemotherapy with S-1 plus cisplatin (CDDP) is now widely accepted as the first line, standard treatment for unresectable and metastatic gastric cancer (1). S-1 (Taiho Pharmaceutical Company, Tokyo, Japan), an oral anticancer agent, consists of tegafur, gimeracil and oteracil potassium at a molar ratio of 1:0.4:1. S-1 has played a major role in the treatment of unresectable and metastatic gastric cancer in Japan. S-1 plus CDDP, S-1 (40–60 mg depending on the patient’s body surface area) was given orally, twice daily for three consecutive weeks, and 60 mg/m² CDDP was given intravenously on Day 8, followed by a 2-week rest period, within a 5-week cycle.

Adjustment disorder, depression and delirium are frequent psychiatric disorders in patients with cancer (2), while hypomanic states are rarely seen during cancer treatment (2–4). In addition, the mechanism underlying the development of hypomanic symptoms has not been fully elucidated. There have been no reports of patients with advanced metastatic gastric cancer experiencing hypomanic episodes during S-1 monotherapy or S-1 plus CDDP therapy. We report an extremely rare case of a patient experiencing hypomanic episodes during treatment with S-1 and CDDP for metastatic gastric cancer with a review of the relevant literature.

CASE REPORT
A 66-year-old woman had undergone distal gastrectomy for advanced gastric cancer at another hospital a year prior to visiting our facility and received adjuvant chemotherapy for 6 months with an oral fluorinated pyrimidine, uracil/tegafur (UFT) (Taiho Pharmaceutical Company). During the postoperative follow-up period, gastric cancer recurrence was diagnosed when she presented with obstructive jaundice and hepatic dysfunction due to lymph node metastasis in the hepatic portal region. Her medical records contained no descriptions indicative of psychiatric disorders during the perioperative period, with outpatient postoperative adjuvant chemotherapy, or during the ~3-week hospital stay when the tumor recurrence was found. After amelioration of jaundice and hepatic dysfunction, she was referred to our hospital for further chemotherapy. S-1 plus CDDP therapy was initiated for unresectable recurrent gastric cancer (with lymph node metastasis in the hepatic portal region) as this is the standard first line treatment for this disease in Japan. She started taking S-1 as an outpatient and was required to stay in the hospital during the CDDP administration period. Her initial hospital stay was uneventful, with no notable adverse events. After discharge from the hospital, she resumed visiting the outpatient clinic (during chemotherapy rest periods).

In the meantime, her son who lived in her neighborhood called to notify us that the patient was acting out of character. According to her son, the patient’s peculiar behavior included using abusive language toward her family members, visiting neighbors at night, attending funerals for people she barely knew and crying without inhibition, starting traffic control duties as a volunteer and undertaking support activity for truant students. Moreover, the patient was rumored by neighbors to have been ‘out of her senses’. On being requested by her family, we retrospectively reviewed her medical chart and found that during her hospital stay and previous outpatient visits, she sometimes intruded into examination rooms when the waiting time at the outpatient clinic was too long and talked about romances unsuitable for her age. In addition, she was frequently missing from her hospital room and seemed to be restless during hospitalization. At her next visit to the outpatient clinic after this contact from her family, she complained of no symptoms, such as pain, and the physical examination revealed no apparent abnormalities. Urine and blood examination findings were normal. Brain and whole body imaging scans showed no abnormalities. There was no evidence suggesting progression of the gastric cancer other than lymph node metastasis. Since no organic abnormalities were found, she was referred for psychiatric consultation to the Department of Psycho-oncology, and underwent a detailed examination by a highly experienced psycho-oncologist.

Present status: The patient was not aware of having an elevated mood and hyperactivity despite having a normal level of consciousness. During outpatient visits, she exhibited flights of ideas, was excessively talkative, highly distractible and tended to speak loudly without pausing for several minutes unless someone interrupted her. She could not stay at home most of the time and was involved in gardening early every morning. Although her family, friends and acquaintances also noticed that these apparent changes occurred after her visits to the hospital, she performed her daily routine/social activities and developed neither psychotic symptoms, such as hallucinations and delusions, nor antisocial behavior including criminality. However, she manifested a distinct period of a persistently elevated, expansive or irritable mood, clearly different from her usual non-depressed state.

Medical history: She had no history of psychiatric disorder or alcohol/drug abuse.

Diagnosis: Her psychiatric features met the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revision (DSM-IV-TR) for hypomanic episodes.

Following this diagnosis, supportive psychotherapy, in which a psycho-oncologist listened attentively to the patient’s complaints, was started. Since her conditions did not require discontinuation of the chemotherapy or additional medications, her cancer treatment was continued along with consultation at the Department of Psycho-oncology.
During the second and subsequent cycles of S-1 and CDDP, no worsening of the symptoms was observed. Currently, she remains on this chemotherapy regimen, which will be continued until disease progression is detected.

**DISCUSSION**

Approximately half of cancer patients reportedly meet the diagnostic criteria for psychiatric disorders with relatively high prevalences for adjustment disorder, depression and delirium (2). The increased occurrence of delirium was also observed in patients with terminal cancer, especially in those requiring inpatient care (5,6). However, it is rare for cancer patients to experience hypomanic episodes (2–4). In addition, the mechanism underlying the development of the hypomanic state has not been fully elucidated. For example, bipolar disorder is characterized by recurrent episodes of manic or depressive moods interspaced with periods of euthymia. Although the occurrence of manic episodes has been suggested to be attributable to an increased dopaminergic drive (7), the underlying pathophysiology of the disease is poorly understood. In recent years, increasing attention has been paid to a possible role of the immune system, including cytokines, in the pathogenesis of psychiatric diseases (8). Such findings may be critical to the understanding of the pathological conditions underlying these disorders.

In the present patient, despite our extensive search for organic abnormalities that might produce hypomanic episodes, no significant changes were found in blood biochemistry or on brain and whole body imaging scans.

In the differential diagnosis of mania, drug-induced hypomania due to S-1 and CDDP cannot be completely excluded. However, even when the time course of symptoms is considered, the causal relationship between the drugs and the episodes remains uncertain due to difficulties in verifying the date of onset of the symptoms. When the patient took UFT as adjuvant chemotherapy after gastrectomy, she had no apparent abnormalities. Since UFT and S-1 are similar oral fluorinated pyrimidines, it seems unlikely that her hypomanic symptoms were attributable to adverse effects of S-1. Our extensive literature search using PubMed and direct inquiry to the manufacturer (Taiho) yielded no reports describing patients with advanced metastatic gastric cancer experiencing hypomanic episodes during S-1 monotherapy or S-1 plus CDDP therapy. In addition, there were no reports on the occurrence of hypomanic episodes attributable to UFT. Hypomanic symptoms in this patient did not improve during the rest period from S-1 plus CDDP therapy, nor was there any deterioration during the second and subsequent cycles of this regimen, suggesting the possibility of a drug-induced manic state to be low. Another possibility besides anticancer drugs that might have induced hypomania was a corticosteroid administered as antiemetic premedication. However, our patient’s hypomanic symptoms neither improved nor worsened regardless of corticosteroid administration; thus, it is unlikely that the corticosteroid might have induced her manic state as is the case with anticancer. Nishimura et al. (9) reported that prednisolone doses >40 mg/day are associated with an increased risk of psychiatric symptoms. Kenna et al. (10), in their review article reported that the mean dexamethasone dose in patients who developed psychiatric symptoms was 9.1 mg/day. The incidence of corticosteroid-induced psychiatric symptoms was found to be dose-related (11,12). Since the dose of dexamethasone administered to the present patient was relatively low (6.6 mg/day), there seems to be little possibility that hypomania was induced by corticosteroid administration in this case.

Although our direct clinical observations of the patient were only made after her referral to the hospital, recurrence of the gastric cancer might have triggered hypomanic episodes. Since she lived alone and her personality before the diagnosis of tumor recurrence was ascertained only by interviews with her family and friends, it was difficult to determine when she developed the hypomanic episodes. She had neither a history of manic and depressive episodes nor a genetic predisposition as indicated by the lack of any family history of mental illness.

Possible mechanisms underlying the onset of her hypomanic episodes would include manic defense. The notion of manic defense, introduced by Klein (13), is a commonly observed phenomenon associated with significantly stressful life events. Although it is rare for cancer patients to show this response, they may experience unbearable anxiety and fear of death, which can trigger psychiatric reactions. Our patient might have manifested manic defense to deny and/or reduce the fear of death accompanied by recurrence of gastric cancer. In the field of psychiatry, funeral mania, a manic episode occurring with the death of an immediate family member, has been explained as a manic defense mechanism. Our patient did not experience the death of a close member of the family or a close friend. Onishi et al. (14), however, have reported a lung cancer patient who experienced a manic episode associated with bereavement on the death of a close friend who had also been suffering from lung cancer.

In our patient, the onset of hypomanic episodes was suspected after we had been contacted directly by a family member during chemotherapy given in our hospital for recurrent gastric cancer. Most of us, as medical oncologists, had recognized that the patient was a very talkative, active person before this contact. Information obtained from third parties was very important for suspecting a psychiatric disorder.

During her second and subsequent cycles of S-1 plus CDDP therapy, no notable problematic behaviors were observed, except for small problems such as laughing loudly and talking to hospital roommates at night. The common medications for manic symptoms include lithium, valproic
acid, carbamazepine, risperidone and olanzapine depending on the severity of the symptoms (15). However, no additional medications were needed to suppress the psychiatric symptoms and she did not cause trouble for medical staff members.

Since there have been no reports of patients with progressive advanced gastric cancer experiencing hypomanic episodes during S-1 monotherapy and S-1 plus CDDP therapy, the present patient seems to represent a rare course. Abusive language and visiting neighbors at night might be indicative of delirium; however, a thorough examination of the patient revealed that her consciousness was clear. When a patient receiving chemotherapy is diagnosed with delirium, treatment may have to be discontinued. Thus, it is extremely important for medical oncologists to distinguish peculiar behavior, as observed in the present patient, from true delirium. Since we could differentiate hypomania from delirium, she could receive further chemotherapy. It may be difficult to diagnose hypomania when patients do not exhibit severe mania requiring inpatient treatment and they can still perform normal social activities without having apparent psychotic symptoms, as in our present patient. Clinicians, however, should recognize the possible development of psychosis or mood disorders in patients receiving gastric cancer treatment. Because of the small number of patients showing hypomanic episodes during cancer treatment, few studies have been performed. Further accumulation of such cases would facilitate elucidating the pathological mechanisms underlying hypomania in cancer patients.

**Conflict of interest statement**

None declared.

**References**