A Case of Prolonged Depression with Tamoxifen


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Abstract
Tamoxifen is known to trigger depressive symptoms as a result of its anti-estrogenic activity. We experienced a patient with a history of depression, who received tamoxifen (an estrogen partial agonist) as a postoperative therapy for breast cancer and developed an relapse of depressive symptoms after about 10 months of treatment. The symptoms aggravated to the state of psychotic depression. This case was poorly responsive to antidepressants and resistant to treatment, but the symptoms improved after interruption of tamoxifen. This observation suggests that tamoxifen may aggravate depression in severe and refractory conditions.

Key words Depression, Tamoxifen, Estrogen, Breast cancer

Introduction
Depressive symptoms accompanying malignant tumors have recently been studied extensively from the standpoint of liaison psychiatry. In particular, several cases of depression have been reported in association with breast cancer, which is a common disease in females.¹,² Although the etiology is not clear, suspected causes include the lowering of self-esteem due to the alteration of appearance and the psychogenic reaction to the disease and to surgical treatment, in addition to the influence of hormonal changes.¹ While anti-estrogens such as tamoxifen are often used to prevent cancer recurrence, this treatment may increase the risk of depressive symptoms.¹ In this paper, we report our experience with a patient who had a history of depression, received tamoxifen after surgery for breast cancer, and then developed severe depression with psychotic symptoms, which became prolonged. To ensure anonymity, details of the patient’s personal information have been modified as necessary.

The Case
Patient: Female, 63 years old.
Genetic factors: Mother committed suicide. Younger sister had depression.
Past history: Tuberculosis at the age of 42, hypertension at the age of 51, breast cancer surgery at the age of 62.
Personality before illness: Meticulous and worrisome.
Life history: The patient was born as the 3rd daughter in a family of 5 children. After graduating from a local high school, she worked for an insurance company as a clerk. After marrying at the age of 23, she mothered 2 children while working part-time.
History of present illness: The patient first visited our department 19 years ago (44 years old) presenting with depressive mood, insomnia, appetite loss, anxiety, thirst, and palpitations. No abnormality was noted in blood counts, biochemistry, etc. Depression was suspected. The symptoms were relieved by treatment with antidepressants for several months, and treatment...
was terminated after about 1 year. Recurrence of depression occurred several times thereafter, but each episode was improved by medication.

Two years ago, the patient received regular screening for breast cancer in the insurance system, and was found to have breast cancer of the left breast. Total mammectomy and axillary dissection were performed in August (61 years old). Histopathological study proved invasive ductal carcinoma, n0, G2, ER(+) , PR(+) , pT0.8 cm. Administration of tamoxifen 20 mg was commenced shortly after surgery, and the progress of treatment was good. Her mental state before and after surgery was stable.

About 1 year ago, in January (62 years old, 5 months from the beginning of tamoxifen therapy), the patient voluntarily stopped taking psychotropic drugs because she felt her condition was good. Outpatient treatment at our department was terminated, ending with the visit in March. She continued to use tamoxifen and hypotensive medication.

In May, the younger sister of the patient was admitted to a hospital for the treatment of depression, and the patient took care of her sister. In June (10 months after the beginning of tamoxifen therapy), the sister was discharged from the hospital. The patient then gradually started to complain depressive mood, loss of motivation, thirst, hypoguesia, lack of concentration, etc., and she revisited our department in early July. Blood counts, biochemistry, and head CT (Fig. 1) revealed no clear abnormality, and the relapse of depression was suspected. EEG was irregular with few alpha waves, suggesting a strained state. The patient remained irregular in the use of drugs. In addition to the abovementioned symptoms, she showed panic attacks, insomnia, appetite loss, and perplexity. Two weeks later, persecutory delusions developed, including the belief that the police and fire fighters would come to collect her debt. The patient was hospitalized for the second time in August.

On admission, the patient was very agitated and perplexed. While her breast cancer had been monitored regularly on an outpatient basis, no recurrence had been noted. Because tamoxifen had been continued, we continued administration after admission. Blood sampling at the time of admission showed slight liver dysfunction (GTP 49 and GPT 61). CK was as high as 1099. The patient was considered to have severe depression, and treatment was started with a drip infusion of clomipramine, an antidepressant. Because delirium was noted and drug-induced delirium due to clomipramine was suspected, the dose was reduced and then stopped. Thereafter, the patient gradually came to show longer lucid intervals.

In mid September, the patient mainly showed depressive symptoms, including depressive mood, appetite loss, and malaise, while abnormal speech and behavior almost disappeared. Blood analysis became largely normal (GOT 20, GPT 21, CK 31). The Hamilton Depression Rating Score was 32. The brain MRI conducted after improvement of disturbance of consciousness demonstrated no abnormality relative to the condition before admission (Fig. 2). EEG indicated improvement, showing a slight increase in the frequency of alpha waves.

Three months later, the patient strongly complained about insomnia. Blood analyses were stable, and the condition was considered to be an aggravation of depression. The Hamilton score was 22, and the persistence of severe depression without psychotic symptoms was inferred. Her condition aggravated further when the patient was temporarily released for regular monitoring of breast cancer. In addition to guilt and suicidal feeling, she started to have delusion of poverty. No recurrence of breast cancer was noted, and tamoxifen was continued.

The condition did not improve for 4 months, and the complaints involving persecution and self-accusation continued. The Hamilton score was 22. The antidepressant was switched to milnacipran 100 mg, and the patient was kept under careful observation.

In January of this year, the patient started to smile occasionally when she was with her family. However, she stayed mostly in bed during the daytime. Her facial expression was stiff, and she expressed suicidal feelings. The Hamilton score was 22, and no improvement of depression was seen.

Because tamoxifen had been suggested to be a cause of depression, we considered the possibility that tamoxifen might affect for the prolonged presence of depression. Following the discussion with the surgeon, tamoxifen was stopped 5 months later. No other changes were made to the regimen, and the patient was kept under careful observation. Within about 2 weeks
after stopping tamoxifen, the patient started to talk more with nurses. Although she described that her condition was “not improving and not good,” she stopped complaining about insomnia. She started to smile during interviews with the physician. Her facial expression improved in about one month, and the patient started to show active behavior, such as walking in the ward. She became able to take a walk with her husband, and to eat meals regularly. Although the patient’s self-evaluation remained poor, evaluation by family members improved and the Hamilton score dropped to 7. The condition clearly improved (Fig. 3).

A different physician was later appointed to take charge of this patient. While aggravation was not seen, remission did not occur and the symptoms became prolonged. Although the main drug was changed to amoxapine and maprotiline, no remarkable changes were observed. Exacerbation did not occur in the course of about one year including several stays at home, and the patient was discharged from the hospital. No recurrence of breast cancer has since been noted, and no abnormality has been shown by monthly blood tests. The brain MRI conducted in October of this year showed no remarkable changes (Fig. 2).

**Laboratory test results:**
- Blood analyses on admission
  - WBC 5800, Hb 12.0, Plt 196,000, TP 5.6, GOT 49, GPT 61, γ-GTP 84, Na 140, K 3.2, Cl 103, CRP 1.25
  - f-T3 2.67, f-T4 0.90, TSH 3.29, ACTH 25.2, cortisol 29.1
- EEG
  - July, last year: Irregular basic pattern with marked presence of beta waves.
  - September, last year: Irregular basic pattern.
  - October, last year: Slow alpha rhythm. Improved appearance of 9–10 Hz alpha waves as compared with the previous data.

**Discussion**

Tamoxifen is a partial agonist of estrogen, which is used as an adjuvant therapy for breast cancer based on the fact that breast cancer cells often have estrogen receptors and the cancer cells are activated by estrogen. Because the partial agonist binds to estrogen receptors in competition with estrogen and its estrogenic effect is weaker than that of estrogen, it exerts an anti-estrogenic effect (Fig. 4). In addition, tamoxifen has various effects such as promoting translation of denatured RNA, reducing cell proliferation, promoting apoptosis of malignant cells, reducing circulation of insulin-like growth factor-I, and increasing circulation of serum hormone binding.
globulin (SHBG) (Fig. 5). These effects are considered to derive from the action of tamoxifen itself, in addition to its anti-estrogenic activity. The possibility that tamoxifen as an anti-estrogen may promote development, severity, and prolongation of depression has not been discussed much in Japan, but this possibility has been pointed out by several authors based on the facts that a decrease in estrogen may cause depression and women often develop depression during the menopause. While there is clinical evidence that estrogen may counter the development of depression, this effect is considered to derive from the positive effect of estrogen on serotonin and noradrenaline. Tamoxifen passes through the blood-brain barrier (BBB) and inhibits these effects of estrogen. It has been reported that depression in patients receiving tamoxifen most frequently occurs within 12 months from the beginning of treatment, in

![Fig. 3 Treatment course](image.png)

![Fig. 4 Antagonism of estrogenic effects by tamoxifen](image.png)
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Fig. 5 Effects of tamoxifen
*: Serum hormone binding globulin

particularly during the period from 3 to 6 months, and dose reduction or termination of tamoxifen usually results in alleviation of symptoms within weeks. The depression related to tamoxifen does not always coincide with climacteric symptoms, which are also major side effects of tamoxifen, and patients with severe depression often lack symptoms such as flushing of the face. These clinical features also suggest the possibility that the development and prolongation of depression related to tamoxifen may not be a result of simple anti-estrogenic activity. The development of depression probably results from the action of tamoxifen itself, in addition to the action mediated by estrogen. The reported incidence rate of depression ranges widely from 1 to 15%. Our search of the literature indicated only 1 paper (by Love) that reported the low level of 1%, and the other 3 studies provided incidence rates in the range from 12 to 16%. The depression in these patients usually improved after dose reduction or termination of tamoxifen in 2 to 4 weeks.

The patient reported here is considered to be a case of recurrent depressive disorder, in view of her past history. Because recurrence of depression did not occur directly following the use of tamoxifen after breast cancer surgery, this case is considered to be an endogenous episode triggered by the psychological pressure caused by hospitalization and home care of her younger sister. As reported by Ishige and Takao et al., aggravation to psychotic depression may occur even 16 months after drug administration. Therefore, the direct involvement of tamoxifen in the pathogenesis of this case may not be ruled out. Past episodes in this patient were characterized by prompt response to antidepressants even when there was severe perplexity. The present episode was unprecedentedly severe, involving psychotic symptoms during the acute phase. Physical illness was excluded by blood counts, biochemistry, thyroid hormone, brain CT, EEG, and other data, and depression improved after the termination of tamoxifen. Because of these facts, it is considered probable that tamoxifen may have affected the severity and prolongation of this episode.

In this case, the dose of antidepressant was not changed during observation for one month after termination of tamoxifen. While depression improved gradually, the improvement was not sufficient to stop administration of antidepressant, and complete remission did not take place. As depression gradually exacerbated 2 months later, the dose of antidepressant had to be increased again. In many previous reports, termination of tamoxifen after development of depression led to improvement in a reversible manner. However, it is not clear whether there are irre-
versible factors. Ishige reported a case that required antidepressant therapy after termination of tamoxifen and continued to have symptoms. We cannot rule out the possibility that the drug was involved in the prolongation of depression after termination of tamoxifen in our case.

Our patient had previously been showing prompt response to tricyclic antidepressants without remarkable side effects. However, in this episode, she developed severe delirium during the use of a tricyclic antidepressant. This could be related to the changes in organic factors, and there has been no report suggesting the involvement of tamoxifen in such alteration of pharmacological effects. However, in view of the timing, such involvement should also be considered as a possibility. More detailed study is needed concerning the use of tamoxifen in patients with depression. Because it may be involved in the severity and prolongation of symptoms, we should be careful regarding the use of tamoxifen in patients with a history of depression.

References