Mania and Psychosis in a Woman Receiving Interferon

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The patient is a 36-year-old married woman diagnosed 7 months ago with stage III malignant melanoma. Following her initial diagnosis, she was started on intravenous interferon-alpha. She subsequently presented to outpatient psychiatry complaining of 3 weeks of psychosis and racing thoughts.

After 5 months of ongoing treatment with interferon, the patient reported visual hallucinations, worsening paranoia, confusion, racing thoughts, and increased anxiety. She noted “obsessions” regarding her 2-year-old daughter’s safety. During this period, she also suffered from significant insomnia, reporting no sleep for 3 days at a time. A prescription for zolpidem 10 mg nightly provided little relief. An MRI ruled out the possibility of central nervous system metastatic disease as an etiology of this new symptom constellation.

The patient denied any history of depression, anxiety, or psychosis. She had never been treated with psychotropic medications, psychotherapy, or psychiatric hospitalizations. She denied any past or current suicidal ideation or self-injurious behaviors. Prior to her diagnosis of malignant melanoma, she was in a state of good health.

She had been treated for hypothyroidism as a teenager and young adult, but had no medication or thyroid studies for the past 3 years. Her most recent available lab results did not include a thyroid-stimulating hormone (TSH) test. She denied allergies to medications, or current drug or alcohol use. Her family history was significant only for a cousin with possible bipolar diagnosis, but no other history of mental illness or substance abuse was noted.

A mental status exam revealed a well-groomed, thin, anxious-appearing woman who was agitated and tearful at times. Her speech became mildly pressured with increased volume. Her mood was “worried, confused.” Her affect appeared labile, intense, and anxious, with a tangential thought process. She denied both suicidal ideation and current auditory or visual hallucinations, but appeared paranoid. Her memory was limited, and clouded for short-term recall.

A trial of olanzapine 5 mg to 10 mg per day was initiated, and follow-up laboratory data were ordered, including TSH, free T4, ammonia, a comprehensive metabolic panel, B-12, and folate levels.

Four days later, the patient’s interferon treatment was postponed by her oncologist, due to ongoing symptoms of psychosis. She continued to exhibit paranoia, anxiety, racing thoughts, and insomnia. She was instructed to increase the olanzapine to 10 mg twice daily. After 3 days, she noted some improvement. She was less anxious and was not experiencing side effects to olanzapine other than dry mouth. She slept through the night for the first time since her symptoms began. Laboratory data were still unavailable.

During the next 3 weeks, the patient continued to experience moderate improvement in her symptoms. Her sleep had improved, but she still suffered from intermittent awakenings. Her appetite had also improved, as evidenced by a 12-pound weight gain, but it was not yet back to her baseline.

Lab testing was done and she was noted to have a markedly elevated TSH of 209.40 uIU/mL (normal range 0.35-5.50 uIU/mL) and suppressed free T4 of 0.12 ng/dL (normal range 0.55-1.43 ng/dL). Other labs, including complete blood count, were within normal range.
Levothyroxine was initiated at 12.5 mcg, followed by a rapid titration to 137 mcg daily.

At the 2-week follow-up, she noted continued difficulty with concentration; however, her mood, paranoia, and sleep all showed signs of improvement. She still experienced delusional thoughts but realized “they are not real. I can let them go.” She was now able to attend to her daughter and went to appointments unassisted. Thyroid studies showed mild improvement with TSH at 202.5 uIU/mL and her free T4 at 0.25 ng/dL.

Three weeks later, the improvement was substantial. She appeared calm, pleasant, and with clear thought. She denied any delusional content. During the next few weeks, olanzapine was successfully tapered and discontinued. Interferon infusions were restarted without recurrence of manic or psychotic symptoms.

**DIAGNOSIS**

**Thyroid Dysfunction**

Thyroid dysfunction commonly presents with multiple somatic, cognitive, and psychiatric symptoms. Depression in the presence of hypothyroidism is well known and may in fact be the initial presenting complaint. Although thyroid dysfunction is found in cases of hyperthyroidism, mania and acute psychosis are relatively rare. Remarkably, studies have shown that between 5% and 15% of patients with myxedema show some signs of psychosis.1

Although a common side effect of interferon treatment is depression, reports of both hypothyroidism and hyperthyroidism in patients treated with interferon-alpha are cited in the literature. Thyroid dysfunction in individuals treated with interferon for carcinoid tumors has been noted in the literature.2 In particular, there are two case reports of sustained hypothyroidism in patients with chronic hepatitis C treated with interferon.3

One factor complicating this diagnosis is that common symptoms of hypothyroidism, including weight gain, constipation, and fatigue, are easily overlooked as a side effect of interferon treatment. This case is unusual in that it presents an individual with chronic, asymptomatic hypothyroidism who developed new-onset mania and psychosis after only receiving 3 weeks of interferon treatment for malignant melanoma.

Case reports of mania and psychosis caused by both hypothyroidism and interferon treatment are rare in the literature. Stowell and Barnhill4 offer an account of a patient with mania and psychosis secondary to postpartum hypothyroidism; the patient’s symptoms rapidly improved with administration of levothyroxine. They also note that treatment with levothyroxine has been shown to be beneficial in refractory bipolar disorder, rapid cycling type.

A case report by Heinrich5 identifies a 73-year-old woman with auditory and visual hallucinations who was found to have a TSH of 43.79 U/mL, with low T3 and T4. Auditory and visual hallucinations cleared after approximately 3 weeks of thyroid replacement therapy. The author also notes that hypothyroidism is a risk factor for developing rapid cycling bipolar disorder, with as many as 50% of rapid cyclers found to be positive for antithyroid antibody titers.5

A literature search of interferon treatment with bipolar mania. Banerjee and colleagues6 reported four patients with resected high-risk melanoma who developed bipolar symptoms or mood instability when treated with interferon therapy. The authors suggest that the risks of mania or hypomania increase when adjusting interferon doses, when treatment with antidepressants is administered, or when interferon therapy is stopped suddenly. They recommend that the patient be followed closely for symptoms of mania for 6 months after discontinuing interferon.

Although the patient’s mania and psychosis were likely precipitated by interferon, the fact that her symptoms only fully abated when thyroid replacement was adequate and not when interferon was held supports our diagnosis that her thyroid disorder, and not interferon treatment, was responsible for her presentation. This is further supported by her ability to tolerate a re-challenge of interferon after euthyroid with no return of mania or paranoid thoughts.

**REFERENCES**