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Manic symptoms in the context of anti-thyroid antibodies and letrozole infertility treatment

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ABSTRACT

A woman in her mid-30s presented to the emergency department upon the recommendation of her obstetrician with manic symptoms after four months of letrozole infertility treatment. Her history of present illness included irritability and increased energy for three weeks. On examination she exhibited distractibility, pressured speech, racing thoughts, and hypergraphia, all of which she noted to be present for at least the past week. Her medical history is significant for Hashimoto's thyroiditis, stabilized with levothyroxine 50 mcg daily, and unspecified depression, for which she has not required treatment in more than five years. Brain computed tomography and thyroid panel revealed normal imaging and normal thyroid stimulating hormone levels, respectively. Thyroid antibody titers were not measured in the emergency department. Syphilis test was negative. She was subsequently admitted for stabilization and accepted risperidone therapy. Manic symptoms started to subside within 48 hours of admission. After some symptom improvement she decided to leave against medical advice with instructions to follow-up with her primary care physician. Upon later referral to an autoimmune neurologist, her thyroid peroxidase antibody level measured high, which was concerning for Hashimoto encephalopathy. EEG showed no abnormalities and corticosteroids were not administered. The patient was tapered off risperidone in the following months with no manic symptom recurrence to date.

1. Summary

A woman in her mid-30s presented to the emergency department upon the recommendation of her obstetrician with manic symptoms after four months of letrozole infertility treatment. Her history of present illness included irritability and increased energy for three weeks. On examination she exhibited distractibility, pressured speech, racing thoughts, and hypergraphia, all of which she noted to be present for at least the past week. Her medical history is significant for Hashimoto's thyroiditis, stabilized with levothyroxine 50 mcg daily, and unspecified depression, for which she has not required treatment in more than five years. Brain computed tomography and thyroid panel revealed normal imaging and normal thyroid stimulating hormone levels, respectively. Thyroid antibody titers were not measured in the emergency department. Syphilis test was negative. She was subsequently admitted for stabilization and accepted risperidone therapy. Manic symptoms started to subside within 48 hours of admission. After some symptom improvement she decided to leave against medical advice with instructions to follow-up with her primary care physician. Upon later referral to an autoimmune neurologist, her thyroid peroxidase antibody level measured high, which was concerning for Hashimoto encephalopathy. EEG showed no abnormalities and corticosteroids were not administered. The patient was tapered off risperidone in the following months with no manic symptom recurrence to date.

2. Background

This case highlights a case presentation of manic symptoms in a patient with a previous history of unspecified depression and Hashimoto's thyroiditis, undergoing letrozole infertility treatment, with positive anti-thyroid antibodies. As such, a differential diagnosis includes Hashimoto encephalopathy and bipolar I disorder.

3. Case presentation

A woman in her mid-30s began letrozole for infertility. The patient has a history of hypothyroidism controlled with levothyroxine 50 mcg daily. Apart from levothyroxine and the newly prescribed letrozole 2.5 mg daily, she also took aspirin 81 mg daily, folic acid 4 mg daily, and an oral prenatal vitamin. Her medical history also includes

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unspecified depression treated with escitalopram during a divorce several years prior to her current marriage. She was tapered off this antidepressant over five years ago. She denied previous manic episodes, substance use disorder, and psychiatric hospitalizations.

During the fourth month of letrozole treatment the patient's obstetrician noticed she was demonstrating irritability and increased energy. She reported having these symptoms for the past three weeks. She also noted feeling angry and frustrated, particularly during the middle of the past letrozole treatment month and around ovulation.

After seeing her obstetrician, the patient voluntarily went to the emergency department where she also reported decreased need for sleep for at least two nights. She presented with hyper-voluminous and rapid speech, and further showed hypergraphia, producing multiple written pages to the emergency department physician. She stated that she "cannot speak fast enough to get the thoughts out, and therefore, has been writing everything down".

The patient had markedly impaired insight and judgement, significant when considering her postgraduate education level. She was difficult to redirect during the exam, showed limited eye contact, and continued to ask "why" throughout the interview. She exhibited disorganized thought but denied hallucinations and suicidal or homicidal ideation. On exam, no delusions were elicited and she did not appear to be internally stimulated. Notably, her husband stated that he had removed all weapons from their home prior to any medical suggestion.

The patient's mother has a history of manic symptoms. However, after treatment for hypothyroidism her mother was no longer symptomatic and did not require psychiatric medication. The patient's father has a history of alcohol use disorder and completed suicide, for which the patient has received grief counseling.

The patient was informed that she met the criteria for court-ordered admission but agreed to voluntary inpatient admission.

4. Investigations

To rule out a metabolic cause for the patient's behavior change, thyroid stimulating hormone (TSH) level was obtained and found to be within normal limits at 2.81 μU/mL. Free T4 was found to be within normal limits at 1.39 ng/dL. Thyroid antibody titers were not measured upon presentation to the emergency department. Tertiary syphilis was ruled out with a negative syphilis screen. Toxicology screen was negative. Brain imaging was also negative. Upon admission, there were no other pertinent findings in the laboratory studies or imaging to suggest a medical condition as the etiology for the patient's manic symptoms.

5. Treatment

The patient was admitted for voluntary inpatient treatment with an estimated seven day length of stay. Letrozole was discontinued and risperidone 2 mg twice daily was given, along with daily maintenance levothyroxine 50 mcg. Within the first 48 hours the patient's manic symptoms began to decrease. However, after 48 hours of treatment the patient was discharged against medical advice.

6. Outcome and follow-up

Upon discharge against medical advice, the patient was advised to follow-up with her primary care physician. After seeing this physician, she was referred to an autoimmune neurologist and psychiatrist. The psychiatrist's primary diagnosis was bipolar I disorder. The autoimmune neurologist discovered an extremely elevated thyroid peroxidase antibody level (296.3 IU/mL), suggesting a diagnosis of Hashimoto encephalopathy. Since her electroencephalogram showed no abnormalities and she had not experienced recurrence of manic symptoms, she did not receive corticosteroid therapy. Over the next several months the patient's primary care physician tapered her off risperidone with no reported recurrence of manic symptoms. To date the patient expresses frustration about receiving multiple diagnoses for this episode, and remains perplexed about this part of her medical past.

7. Discussion

The patient presented with what appeared to be signs and symptoms of a manic episode occurring in the context of letrozole infertility treatment. It is helpful to consider that mania defined by DSM-5 requires one week of manic symptoms present most of the day. According to the DSM-5 manic symptoms are "abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity" that must be enough to cause "marked impairment in social or occupational functioning or to necessitate hospitalization" [1]. The patient in this case exhibited increased energy, pressured speech, irritability, and hypergraphia, which caused her to produce multiple written pages of her thoughts for at least one week. Nothing like this had ever happened to her before. The physicians treating her ultimately decided that hospitalization was the best course of action to stabilize the patient during this episode.

DSM-5 also indicates that mania's definition includes symptoms that must not be "attributable to the physiological effects of a substance or to another medical condition" [1]. In this patient's case it is unclear whether her manic symptoms were caused by the first occurrence of a manic episode, perhaps as part of bipolar I disorder, by the medication she was taking at the time (letrozole), a medical condition (Hashimoto encephalopathy) or some combination thereof.

Bearing in mind that the patient's history includes Hashimoto's thyroiditis, an autoimmune response induced by letrozole is possible. Current literature includes cases of aromatase inhibitors (the broad class of drugs to which letrozole belongs) associated with the new presentation of autoimmune processes. In one case, authors argue the association between a third generation aromatase inhibitor and a diagnosed case of Sjogren syndrome in a woman receiving treatment after breast cancer [2].

In our patient's case, the autoimmune process triggered was likely Hashimoto encephalopathy. The clinical presentation of Hashimoto encephalopathy shows varied neurological symptoms, such as the manic symptoms seen in our patient. Importantly, this condition results from autoimmunity and not hypothyroidism or hyperthyroidism. Lab studies will show that the patient is euthyroid with elevated antithyroid antibodies, which is consistent with our patient's results from her visit with an autoimmune neurologist. Since Hashimoto encephalopathy is a rare condition, further testing and imaging is used to rule out other causes of neurological symptoms. For example, our patient underwent electroencephalogram and additional blood work to exclude a source of infection as causative agent.

The treatment of choice for Hashimoto encephalopathy is corticosteroids [3]. Positive response with resolution of symptoms is helpful in making the definitive diagnosis of Hashimoto encephalopathy. Since our patient's electroencephalogram showed no abnormalities and her condition remained stable, the treating physician felt corticosteroids were not necessary in her case. As a result we do not have a documented response to a course of corticosteroids. However, since the neurological symptoms of Hashimoto encephalopathy are quite varied, acceptable treatment includes medications to address presenting symptoms. In our patient's case risperidone was used to decrease manic symptoms.

It is clear that stopping letrozole and starting risperidone was helpful for our patient. Since risperidone remains an acceptable treatment for the acute mania of bipolar I disorder as well as for symptoms of Hashimoto encephalopathy, it is difficult to definitively separate the two diagnoses. Indeed, our patient meets diagnostic criteria for both bipolar I disorder (if the manic episode was not caused by a medical condition or substance) and Hashimoto encephalopathy. To our knowledge the patient is no longer receiving risperidone or any other psychiatric treatment and has not had a recurrence of manic symptoms.

However, if a diagnosis of bipolar I disorder is accurate, it would be important for her to receive early treatment as this disorder is associated with a comparatively high risk of suicide and significant morbidity. If a diagnosis of Hashimoto encephalopathy is accurate, there is a fair chance that our patient will experience a disease course marked by relapsing and remitting symptoms [3].

8. Learning points/take home messages:

- Infertility treatment requires careful and regular monitoring by a multidisciplinary team of health care providers.
- Hashimoto encephalopathy occurs while the patient is euthyroid, making it important to check anti-thyroid antibodies.
- Clinicians should maintain a high index of suspicion for an autoimmune response to treatment, particularly in patients with prior history of an autoimmune disease.
- When diagnosing psychiatric disorders, clinicians must remember to first exclude a medical condition or effects of a substance.
- Early diagnosis of bipolar I disorder has important implications for decreasing the risk of suicide and minimizing morbidity associated with the disorder.

9. Patient's perspective

It's difficult to briefly describe how this has affected me. I have dealt with a lot of anger at my OBGYN for not listening to me when I was describing my symptoms leading up to my manic episode. Prior to my admission, I was having increasing irritability on letrozole which he dismissed. As a health care professional myself, and being married to a physician, I was extremely upset and embarrassed once my mania had subsided and I realized I was admitted to a psych facility, which is why I chose to leave AMA. It was incredibly hard to be around schizophrenic patients and not be able go outside for days. Regarding details on my post-hospitalization course, the night I left AMA I was given my dose of risperidone prior to leaving. Before I could even make it home, I had extra-pyramidal side effects where my mouth involuntary puckered up and I could not breath very well. My husband quickly gave me Benadryl and the side effects resolved. From then on, I took Benadryl with the 2 mg dose of risperidone to prevent this.

I left AMA, therefore no prescriptions or follow up appointments were given to me. I made sure to contact my PCP, who took over the risperidone prescription until I could see a psychiatrist and I also made appointments to get in with a counselor. I did eventually see an outpatient psychiatrist, who made a diagnosis of bipolar I. Over the course of a few months, my risperidone dose was decreased to 0.5 mg because of involuntary retching, loss of appetite, lethargy, and weight loss of 20 pounds. I became increasingly and severely depressed. My PCP checked all my hormone levels and my prolactin level came back at 130. He then ordered an MRI of my brain in which they found a micro pituitary adenoma. Because my risperidone dose was so low, he weaned me off, rechecked my prolactin levels, which had come back to normal, and then my depression subsided once I was off the risperidone.

My only past medical history is Hashimoto's thyroiditis. So, I still remain confused on my actual diagnosis because my hospital discharge diagnosis was drug-induced psychosis. Then a bipolar I diagnosis from my psychiatrist. Then a diagnosis of Hashimoto's encephalopathy from an autoimmune neurologist. I am now off all anti-psychotic medications, my mood is stable and I continue to see my counselor and psychiatrist. As a 36-year-old female that was just trying to start a family, I still question whether or not I actually have bipolar disorder or if all of this was reactions to medications since I have had no mood episodes like this in my teenage or adult life.

What I would hope physicians can learn from my case is to listen to your patients when they are describing their symptoms. I understand physicians deal with certain drugs all time, but to patients, they are new and can be intimidating.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2019.01.003.

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