Depression During Hormonal Treatment Of Prostate Cancer

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Prostate cancer is the most common malignancy in men, with the majority of cases detected after the seventh decade.[1] In the past treatment consisted of testosterone deprivation by orchiectomy or treatment with estrogen analogs. The recent introduction of the gonadotropin-releasing hormone analog, leuprolide, has made possible chemical castration by once-a-month intramuscular injection.[2] Leuprolide is therefore being widely used. We report 3 patients who developed depression after initiation of leuprolide therapy.

Case Reports

The Turner Geriatric Clinic is a medical school-based outpatient facility that provides primary and consultative geriatric care. All 3 patients were cared for by one of the authors (DER). All dates are given relative to the first patient visit at Turner Geriatric Clinic.

Case 1

A 76-year-old man had a history of alcohol abuse but had been sober for the previous 17 years. His chronic medical problems were chronic obstructive pulmonary disease, atrial fibrillation, congestive heart failure, hypertension, asthma, chronic sinusitis, and incontinence secondary to a transurethral prostate resection. Three months before he came to the geriatric clinic, a stage D, Gleason 7, prostatic cancer had been diagnosed, and he was prescribed leuprolide and flutamide. Two months later he developed symptoms of major depression, with sad mood, agitation, sleep disturbance, and suicidal ideation. His depression was treated with bupropion, 100 mg three times a day, and lorazepam, 1 mg three times a day. When he first came to the clinic, he was still severely depressed. His medications at the time of his first visit are shown in Table 1. Bupropion and lorazepam were continued for the next 3 weeks, but he had minimal response, so leuprolide was discontinued. Within 1 month his depressive symptoms improved considerably, and his condition was successfully maintained with bupropion, 75 mg three times a day, and flutamide for the next 3 months. His antidepressant therapy was then changed from bupropion to doxepin, and leuprolide was again prescribed. Shortly thereafter his depressive symptoms returned. His antidepressant medication was briefly switched back to bupropion. Subsequently he developed gynecomastia and discontinued, on his own, the bupropion, leuprolide, and flutamide. His depressive symptoms completely resolved within weeks and have not recurred in the succeeding 24 months.

Case 2

An 84-year-old man had no previous psychiatric history. His chronic medical problems were hypertension, atrial fibrillation, recurrent gastrointestinal bleeding from a gastric ulcer and duodenal diverticula, urge incontinence, and a chronic pain syndrome secondary to multiple fractures he received in a motor vehicle accident that left him dependent on narcotics and severely debilitated. He also had residual right-sided sensory deficits as a result of a left cerebral hemisphere cerebrovascular accident. Eight months before he came to the clinic, a prostatic carcinoma, stage B2, Gleason 5, was diagnosed. He was asymptomatic from the cancer at the time of his initial visit, but he was debilitated and narcotic dependent as a result of chronic pain. During the next several months he was weaned from narcotics almost entirely and made considerable progress in his activities of daily living and instrumental activities of daily living despite recurrent hospitalizations for medical problems. During the course of these hospitalizations, he was examined by the consultant psychiatrist, who thought

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that the patient was only mildly depressed to a degree consistent with his medical illness.

Nineteen months after his initial visit to the clinic, he was prescribed leuprolide to treat a rise in prostate-specific antigen. His other medications at this time are shown in Table 1. During the next several months his wife noticed a pattern of acute diarrhea for 1 day and of crying fits for about 1 week after each leuprolide injection. The duration of the crying spells increased during the 9 ensuing months, and he finally came to the clinic again, debilitated, depressed, tearful, complaining of total body pain and with his wife complaining of hypersomnolence. He was prescribed 10 mg of desipramine. During the next 4 months repeated efforts were made to adjust his psychotropic medication, but because of his frail state, he was unable to tolerate any increase in his desipramine dosage or attempts at treatment with other antidepressants. Leuprolide was therefore discontinued, and within 6 weeks his depression completely resolved, as did his complaints of total body pain, and he again began participating in physical therapy. The depression recurred when leuprolide therapy was resumed 8 months later. The patient had a partial response to methylphenidate, but at the time this report was written, he had elected to once again stop the leuprolide therapy and was experiencing marked improvement in mood.

Case 3

An 81-year-old man with a history of dementia and depression was found to have stage C-D, Gleason 8, prostatic cancer 2 weeks before his initial clinic visit, and he developed a worsening of his depressive symptoms with severely depressed mood, weight loss, and suicidal ideation in spite of treatment with alprazolam. In the Turner Geriatric Clinic the diagnoses of dementia (Mini-Mental State Examination = 12),[3] anxiety, and depression were made; his dosage of alprazolam was tapered; and the patient's mental condition was successfully treated with nortriptyline, 20 mg two times a day, and lorazepam, 0.5 mg four times a day. Two months later he was prescribed leuprolide because of an elevated prostate-specific antigen, and the lorazepam dosage was tapered to 0.5 mg a day. The patient experienced an episode of confusion after the first daily injection of leuprolide. He had no confusion after subsequent injections, so he was prescribed monthly leuprolide injections. He did well for about 2 months but then developed recurrent depression that peaked 1 week after each injection and slowly declined during the course of the month. Medications at this time (Table 1) included nortriptyline and lorazepam. This depression did not respond well to an increase in tricyclic antidepressant therapy to 60 mg a day or to lithium augmentation at 300 mg every day. Ten months after the initiation of leuprolide therapy, he became delirious and all medications were stopped including the leuprolide. His depressive symptoms resolved 8 weeks after the termination of the leuprolide therapy, although he continued to have progressive cognitive impairment consistent with a diagnosis of Alzheimer disease. There was no recurrence of his depression in the 22 months that preceded his death, although he was prescribed intermittent lorazepam for anxiety.

Discussion

All 3 patients developed depression after initiation of hormonal therapy aimed at lowering testosterone levels. The timing of the onset of the depression suggests that it was related to the hormonal therapy rather than to the patient receiving a cancer diagnosis, and in cases 2 and 3 hormonal therapy was initiated long after the diagnosis. In case 1, where the diagnosis and treatment were

Table 1. Medications at Onset of Depression.

Case 1	Case 2	Case 3
Albuterol inhaler (Ventolin)	Diltiazem	Lorazepam
Triamcinolone inhaler (Azmacort)	Hydrochlorothiazide-triamterene (Dyazide)	Nortriptyline
Potassium, extended-release (K-dur)	Acetaminophen and codeine (Tylenol #3)	Leuprolide
Theophylline (Theo-dur)	Desipramine	
Lorazepam	Leuprolide	
Digoxin		
Furosemide		
Lisinopril		
Warfarin (Coumadin)		
Bupropion		
Flutamide		
Leuprolide		

closely linked, the patient recovered from his depression on cessation of hormone therapy and relapsed into depression with reinitiation of hormonal therapy. In fact, depression resolved in all 3 men when leuprolide was stopped and recurred in both cases 1 and 2 when hormonal therapy with leuprolide was reinstated.

Each patient had several other factors that could have predisposed him to depression. The patient in case 1 had a history of alcoholism, which is associated with major depression.[4] He also had a heavy burden of illness that limited him from participating in his favorite activities and that resulted in several hospitalizations. In case 2, the patient also had severe medical problems that resulted in recurrent hospitalizations, in addition to chronic pain syndrome, which often can have a depressive component, although a full depressive syndrome did not emerge until leuprolide therapy was initiated. In case 3, the patient had a history of cognitive impairment and mood symptoms.

We suggest that these conditions might have predisposed these patients to depression in the face of hormonal manipulation. The close connection between onset of treatment and onset of depression supports the idea that the leuprolide therapy triggered the depression. Furthermore, all of the patients had resolution of their depressed mood after cessation of leuprolide therapy in spite of having on-going or increasingly severe medical problems. The recurrence of depression in the two cases rechallenged with leuprolide strongly supports a role for this hormonal manipulation in precipitating the depression.

The limbic-hypothalamic-pituitary-gonadal axis is known to be involved in psychiatric illnesses.[5] Although much of the study of sex hormones and mood has focused on female hormones, there are a number of studies on testosterone in depression. There are several reports of decreased testosterone in depressed men, particularly older men, compared with age-matched controls.[6-8] Other reports suggest that testosterone levels increase after resolution of depression.[9,10] It is not clear whether this is a causal or secondary effect of depression, and a review of the debate on the pathophysiological role of testosterone in depression is beyond the scope of this report.

The patients in this case report clearly had an onset of depression after pharmacological treatment to lower testosterone levels. While the data reported here are suggestive, much more clinical and research data are certainly needed to arrive at a clear understanding of the connection between testosterone lowering and depression. Indeed, a definitive explanation of the interaction between sex hormones and neurotransmitters in the pathogenesis of depression remains a major goal of psychophysiological research.

While awaiting such studies, clinicians should bear in mind that prostate cancer is a common disease and that hormonal therapy with growth hormone releasing hormone agonists has become a common practice. Many patients who will receive hormonal therapy will have risk factors for depression similar to those in the cases reported here. It is therefore important that physicians monitor patients for depression during the course of hormonal therapy. Screening for depression is especially important for cases in which the severity of the depression might not match that reported here, and so might be less obvious but still have considerable impact on the patients' quality of life. Administering the Geriatric Depression Screen (GDS)[11] and pursuing the diagnosis of depression in any patient scoring 5 or more are useful ways of screening for depression in these patients.

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