New-onset psychosis following androgen deprivation therapy for prostate cancer

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Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer and is associated with several side effects including psychiatric disorders. We present an unusual case of a 62-year-old man with high risk prostate cancer that developed de novo psychosis after starting luteinizing hormone-releasing hormone (LHRH) agonists and discuss possible mechanisms to explain such findings. This case report highlights the importance of continuing assessment and monitoring of potential emotional and behavioral symptoms in prostate cancer patients treated with ADT.

Key Words: prostate cancer, androgen deprivation, psychosis, triptorelin, LHRH agonist

Introduction

Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer and is associated with several side effects including the development of psychiatric disorders. In addition, de novo psychosis is an extremely rare complication that arises in < 1% of men receiving luteinizing hormone-releasing hormone (LHRH) agonist during prostate cancer therapy. Here we present an unusual case of de novo psychosis following LHRH agonist in a prostate cancer patient and discuss possible mechanisms.

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Case report

Mr. H is a 62-year-old man that was found to have an elevated prostate-specific antigen (PSA) of 38.19 ug/L and an enlarged prostate gland with extra-capsular extension on digital rectal. A transrectal ultrasound biopsy revealed prostatic adenocarcinoma in 8 out of 10 samples with predominantly Gleason score 9 (5+4) involving between 10%-100% per core. Full metastatic work up was negative for distant metastatic disease. He was diagnosed with high risk adenocarcinoma of the prostate as per D'Amico classification[1] and was to be treated with neoadjuvant, concomitant, and adjuvant ADT (triptorelin 11.25 mg I.M. q3 months; ADT) and external beam radiation therapy (72 Gy/36 fractions, 18MV photons).

Mr. H began to experience insomnia, irritability, and anhedonia 4 weeks after initiation of Triptorelin and subsequently developed paranoid delusions.

For example, he commented to his wife on several occasions that he thought his friends wanted to harm him. In addition he began to think that his daughter and wife were colluding with doctors to poison him. He also started to believe that his wife was having an affair. Three weeks later he became aggressive and demonstrated impulsive behaviors that ranged from choking his daughter to lunging to grab a butcher knife. His family, then, took him to the emergency department where he was found to have a psychotic syndrome with no insight, poor judgment, euthymic mood, and blunted affect. On work up his total testosterone level was 0.56 nmol/L (2.80-21.60 nmol/L), PSA was 9.28 µg/L (0.00-4.00 µg/L), and a computerized tomography (CT) scan of his head was normal.

After psychiatric assessment his axis I diagnosis was major depressive disorder (MDD) with psychotic features, axis II nil, axis III contribution from ADT, axis IV prostate cancer, and axis V global assessment of functioning was 45-50. Mr. H was started on citalopram 10 mg p.o. q.d. and olanzapine RD 5 mg p.o. q.d. His citalopram was gradually increased to 20 mg p.o. q.d. and his olanzapine RD was unchanged at time of discharge. However, Mr. H returned to hospital within 24h after refusing to take his medications and having re-experienced his paranoid ideations. He was later admitted to a psychiatric ward and his olanzapine RD was gradually increased to 20 mg p.o. q.d while his citalopram 20 mg p.o. q.d. was discontinued. Subsequently, a diagnosis of psychotic disorder with paranoid delusions was affirmed.

Regarding his ADT, triptorelin was switched to goserelin and he eventually completed his radiation treatment. However at 8 months post ADT he relapsed once again and was eventually admitted to a psychiatric hospital for 1 month. At that time his testosterone level was 0.91 and PSA was 0.91. His olanzapine was initially increased to 20 mg and then decreased to 15 mg q.d. In addition he was prescribed aripiprazole 2 mg p.o. q.d. The patient remained psychiatrically stable with testosterone at 13 and PSA at 0.8 at 2 year follow up.

Discussion

To our knowledge, this is the first case report describing de novo psychosis after starting triptorelin, a decapeptide agonist of LHRH, in a man with prostate cancer. Triptorelin, which is commonly used in high risk and advanced prostate cancers, initially causes a rise in testosterone (peak days 2-3) followed by a gradual decline to low levels (3-4 weeks). It is also sometimes used off-label to treat endometriosis, in vitro fertilization, precocious puberty, and uterine sarcoma. Common adverse reactions consist of hot flashes (59%-73%), anemia (> 10%), skeletal pain (21%), headache (14%), and constipation (15%).[2]

There are several clinical reports that support our findings. For example, a retrospective study that investigated 395 prostate cancer patients treated with goserelin, also a LHRH agonist, found that 101 subjects (27.9%) developed new psychiatric conditions. Among these 101 subjects, 2% developed psychotic depression and 1% developed psychosis only.[3] In addition, a case report on a 32-year-old woman undergoing treatment for endometriosis, described the onset of schizoaffective disorder after 2 months of triptorelin therapy.[4]

Several molecular neuroanatomical mechanisms that alter catecholamine and indolamine pathways can also explain the clinical findings. For example, animal studies show that gonadectomy in adult male rats correlates with increased monoamine synthesis and alters the affinity of their receptors, further promoting intracellular signaling cascade activation.[5] In addition, gonadectomy in rodents correlates with changes in tyrosine hydroxylase-immunoreactive axon density in various prefrontal regions of the rat cerebral cortex,[6,7] which can be inhibited with estrogen or testosterone supplementation. These findings suggest that a decrease in testosterone levels can alter dopamine system in the prefrontal cortex, which is one of the mechanisms proposed to be associated with psychotic behavior.[8] Another potential mechanism associated with the development of psychosis following ADT is through modification of monoamine oxidase-A (MAO-A) receptor expression. For example, several androgen response elements exist in the human MAO-A gene,[9] which suggests that the expression of MAO-A can be directly influenced by changes in androgen levels. More recently, it has been demonstrated that gonadectomy increases the activity of MAO-A, but not MAO-B, in the prefrontal cortex of adult male rats, which can be reversed by administration of testosterone.[5]

In conclusion, our report highlights the importance of continuing to assess and monitor for emotional and behavioral symptoms in prostate cancer patients treated with triptorelin or other forms of ADT. It also suggests that treatment with atypical antipsychotics may benefit patients with new onset psychosis following ADT. Prospective studies examining the long term course of psychosis triggered by ADT therapy are warranted. □

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