Tardive Dyskinesia Associated With Anastrozole

To the Editor: Tardive dyskinesia (TD) is very well known side effect of typical antipsychotics. However, it is rarely reported with anti-cancer medication. We report a first journal case of TD in 48-year-old-woman who has been on anastrozole for the last 3 years for carcinoma of the breast. We postulate that the central aromatase inhibition of anastrozole leads the compensatory up-regulation of postsynaptic receptors, supporting the dopamine supersensitivity hypothesis of TD. Oncologists and neurologists should be aware of this side effect, which may occur with long-term use. We also suggest the inclusion of the Abnormal Involuntary Movement Scale to assess TD in all prospective clinical trials of anastrozole.

Tardive dyskinesia is an abnormal involuntary hyperkinetic disorder that occurs during or shortly after the termination of offending agents, commonly in long-term use of typical antipsychotics.[1,2] It may affect any part of the body; the tongue and oral area are most commonly affected. The main concerns are disability and its potential irreversibility even after stopping the offending drug.[3] Other medications, such as oral contraceptives, chloroquine,[4] and selective serotonin reuptake inhibitors[5] have reportedly been associated with TD. Reports of TD with anti-cancer medication are lacking.

Anastrozole is frequently used in the treatment of carcinoma of the breast. This is an anti-estrogen drug that reversibly binds the aromatase enzyme through competitive inhibition, inhibits the conversion of androgen to estrogen in peripheral tissues (mostly adrenals), thereby lowering estrogen levels at a few sites of central nervous system in various regions of brain.[6]

A use-community website claims that there are report of three cases of TD on anastrozole from the FDA.[7] However, we could not trace the reports in any scientific journal. We report a case of TD in a female patient who was on anastrozole for the last 3 years.

Case Summary

A 48-year-old married woman from a higher socio-economic status, with an urban background, presented with past history of having undergone modified radical mastectomy and 6 cycles of FAC (5-fluorouracil, Adriamycin A, and cyclophosphamide) regimen chemotherapy, followed by radiotherapy 6 years earlier for carcinoma of the right breast. She was on adjuvant tamoxifen 20 mg OD for the first 3 years, followed by anastrozole 1 mg OD for the last 3 years, along with calcium supplementation. She also underwent total abdominal hysterectomy, with bilateral salpingo-oophorectomy 2½ years earlier for a fibroid uterus pressurizing urinary bladder. She is regularly undergoing mammography. For the last 9 months, she has been receiving injection Zoledronic Acid 4 mg in 100 ml saline, once in 6 months for osteopenic changes in the hip, spine, and ulna. There is no other medical or psychiatric illness, and she has not been exposed to psychotropic medication. Personal and family histories were also not significant.

She presented with the chief complaint of abnormal involuntary movements (AIM) around her mouth, involving the lips, jaw, and neck muscles for the last 1 month. This AIM was noticed by the patient herself as it was causing obstruction in the movement of the lower jaw, with clenching, biting, protrusion, and retraction of the jaw during conversation. Subsequently, family members also noticed these movements while she was speaking. Movements increase with anxiety, disappear during sleep, and can be voluntarily suppressed for awhile.

On examination, AIM consisted of slow, writhing choreo-athetoid movements, predominantly involving the muscles of the jaw, facial expression, and peri-oral regions. Her speech production was also disturbed. Patient also had contraction of platysma, with compensatory clenching of teeth during conversation. Otherwise, no abnormality was detected in systemic examination.

Computed tomography of brain, thyroid profile, Wilson disease work-up, along with routine biochemical and hematological parameters found no abnormality. Detailed psychiatric evaluation ruled out a functional component. Diagnosis of tardive dyskinesia (TD; DSM-IV) due to anastrozole was considered. The rating of the AIMS (Abnormal Involuntary Movement Scale)[8] showed the severity as moderate at lips and peri-oral area, mild at muscles of facial expression, minimal at tongue, and moderate in all items of global judgments (severity of abnormal movements overall, incapacitation due to abnormal movements, and patient's awareness of abnormal movements).

On advice of the medical oncologist, the anastrozole was stopped. In treatment, clonazepam 0.5 mg/day was started, with an aim to providing some relief in obstructive movements of the mouth. After

2 days, tetrabenazine was added, up to 25 mg/day. Patient was discharged on these medications with advice for regular follow-up to monitor her TD and carcinoma breast. One week later, on follow-up, patient had slight worsening in her clinical condition, for which the dose of tetrabenazine was slowly increased to 100 mg/day.

Discussion

It is reasonably common to observe TD with older neuroleptics. However, it is uncommon with anticancer drugs, especially anastrozole. After exclusion of all possible causes either by history (absence of family history of movement disorders, past history of never been exposed to any neuroleptics) and investigations in the presence of exposure to anastrozole for last 3 years, we concluded that the patient had anastrozole-induced TD.

Among the etiological hypotheses of TD, the dopamine supersensitivity hypothesis[9] is the best explanation in this case. Along with peripheral inhibition, anastrozole causes central aromatase inhibition.[6] This central inhibition causes exacerbation of strial susceptibility to dopamine neurotoxin.[10] On prolonged use of anastrozole, we may postulate that this chronic dopamine depletion leads the compensatory up-regulation of postsynaptic receptors that might have caused TD. However, since it was obstructive during eating and speaking, the patient approached clinicians for help early.

We report the first case of TD with anastrozole in a scientific journal. Clinicians, especially oncologists and neurologists, should be aware of this side effect, which may occur with long-term use. The authors suggest inclusion of the AIMS in all prospective clinical trials of anastrozole.

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