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Letter to the Editor: Brief Case Report

Catatonia Following Autologous Tumor-Infiltrating Immunotherapy and Interleukin-2 Infusions: A Case Report

Introduction

Catatonia is a complex neuropsychiatric syndrome marked by mutism, stupor, posturing, echophenomena, negativism, stereotypy, waxy flexibility, and ambitendency. Early diagnosis of catatonia is essential for timely intervention. If left untreated, symptoms can result in various medical complications, ranging from severe deconditioning to aspiration pneumonia, and may even be life-threatening. While many theories exist, the etiology of catatonia is still unclear. It is primarily associated with psychiatric disorders; however, it is also observed to originate from various medical causes.

Cancer immunotherapy involves using the immune system against cancer cells, and as a field, it has expanded treatment for many previously inoperable tumors. Adoptive cell transfer of autologous tumor-infiltrating lymphocytes (TILs) involves removing an individual's own immune cells, manipulating them to respond directly to the target cells, and then administering them back into the individual.[1] Interleukin-2 (IL-2) is a cytokine involved in T-cell growth, activation, and differentiation that can stimulate regression in certain cancers.[2] IL-2 therapy is known to be associated with risk of neurotoxicity.[3] Mild symptoms typically present as insomnia and restlessness and can be mitigated with benzodiazepines. Severe neurotoxicity has been observed to include personality changes, hostility, delirium, and hallucinations, at times requiring antipsychotic intervention.

While there are many examples of catatonia associated with autoimmune conditions and encephalitis, few articles have recorded associations with immunotherapy treatments. We describe a unique case of catatonia following treatment with TIL and IL-2 as part of a phase II research protocol.

Case Report

Mr. AB is a 59-year-old male with a history notable for remote mild depression, recurrent metastatic oropharyngeal carcinoma, and no active substance use. He was admitted to the hospital for an 8-day protocol that included lymphodepletion with cyclophosphamide and fludarabine, then infusion with TIL and 6 doses of IL-2, with several doses of intravenous meperidine for pain (total of 112.5 mg in 24 hours with normal renal function). The evening following completion, he experienced mild visual and tactile hallucinations that lasted 2 days, without other symptoms of delirium or psychosis. The hallucinations resolved before discharge and were attributed to either meperidine or TIL cells.

He appeared close to baseline at discharge; however, he exhibited increasingly unusual behavior his first evening at home. He was brought to the emergency department, where he was found to be hypertensive to 170/60s, tachycardic to 170s, and afebrile. Self-dialoguing, repetitive movements, and freezing were observed. Complete metabolic panel, complete blood count, thyroid studies, and viral serology were noncontributory, and urine toxicology was negative. He was admitted to oncology, given 35-mg intravenous dexamethasone in the first 24 hours, and initiated on intravenous levetiracetam for suspicion for immunotherapy neurotoxicity and reduced seizure threshold. Psychiatry was consulted on hospital day two for altered mental status.

Vital signs normalized although he continued to have diminished sleep, poor oral intake, and urinary incontinence. On evaluation by psychiatry, Mr. AB scored 16 on the Bush-Francis Catatonia Rating Scale for symptoms of immobility, mutism, staring, posturing, echolalia, verbigeration, negativism, waxy flexibility, and withdrawal. Magnetic resonance imaging of the brain with and without contrast, lumbar puncture, and spot electroencephalogram were unrevealing.

A 2-mg intravenous lorazepam trial was initiated with modest improvement. Scheduled lorazepam was started and titrated to 1.5 mg 3 times daily with dramatic results. After several days of therapy, he was close to his cognitive baseline and was discharged on a lorazepam

taper. He was tapered off lorazepam in the subsequent months and did not have recurrence in catatonia symptoms.

Discussion

This case highlights catatonia as a potential adverse effect from TIL and IL-2 infusions in cancer treatment. The temporal proximity of symptom onset to treatment with TIL and IL-2 supports a potential connection. There is a known association between aberrations in proinflammatory cytokines and psychiatric illness, including soluble IL-2 receptors.[4] In general, an elevation in proinflammatory cytokines can result in a hypoactive motor state, such as catatonia, and the neurotoxic effects of an inflammatory response may well be responsible for the catatonic state.[5] Systemic inflammation would represent a more unusual mechanism, as most nonpsychiatric presentations of catatonia are related to infectious or autoimmune processes.[5] Interestingly, however, there was no meaningful response to systemic steroids. An infectious etiology was considered; however, medical workup was unrevealing. Other key features of this case include the patient's lack of previous psychiatric history other than mild depression, treated more than 25 years prior with an unknown antidepressant, as well as the quick onset of symptoms. As it only depicts a single event, the generalizability of risk of catatonia associated with these therapies is unclear. However, the rapid improvement in symptoms and effectiveness of treatment with lorazepam alone is encouraging for future cases. To our knowledge, there have been no other reports of catatonia resulting from IL-2 infusion. This case uniquely describes catatonia as an adverse event associated with cancer-focused immunotherapy.

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