Adult-onset adrenoleukodystrophy presenting after chemotherapy

No black and white matter

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A 43-year-old right-handed man presented after 6 months of subacute cognitive decline following chemotherapy treatment for multiple myeloma. His initial presentation of hematuria was assessed with serum protein electrophoresis and ultimately bone marrow biopsy. Prior to this diagnosis, he was functioning well at his job as a salesman, but 2 months after diagnosis, he noticed difficulties performing calculations and had increasing visuospatial symptoms (e.g., he became lost while driving on several occasions). He then began a 6-month chemotherapy regimen of bortezomib, lenalidomide, and dexamethasone. Over the next 4 months, he noted increasing difficulty processing information at work, necessitating him to take disability leave. Brain MRI with and without contrast demonstrated symmetrical subcortical confluent white matter changes on T2 and fluid-attenuated inversion recovery images with subtle contrast enhancement in the posterior corpus callosum (figure). The patient was referred to neurology clinic with concerns of chemotherapy-induced leukoencephalopathy.

Examination was notable for simultagnosia, optic ataxia, and optic apraxia, as well as ideomotor and ideational apraxia. On further history, he reported several maternal male relatives, including a maternal uncle, a maternal aunt's son, and a maternal grandmother's male relative, who had died prematurely following gradual decline in cognition. Most germane was a report that his 40-year-old maternal cousin was recently admitted to a psychiatric hospital in a neighboring state, with "psychosis and dementia," with symptom onset 3 years prior. Indeed, his cousin's brain MRI was also notable for diffuse white matter changes (figure).

The family history (X-linked nature), along with the pattern of posterior white matter changes, prompted evaluation for adrenoleukodystrophy, and very long-chain fatty acid (VLCFA) levels were consistent with this diagnosis. CSF studies were unremarkable. A cervical, thoracic, and lumbar spine MRI showed no abnormalities. Evaluation for adrenal insufficiency was clouded by the patient's treatment with dexamethasone as part of his chemotherapy protocol. Genetic testing unveiled a pathogenic mutation in the *ABCD1* (adrenoleukodystrophy) gene (cytosine to thymine change at location 838). Over the following year, the patient

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Figure Brain MRI of patient and first cousin

Brain MRI without contrast of patient (A–C) and his cousin (D–F): T1 postcontrast (A, D), fluid-attenuated inversion recovery (B, E), and T2 (C, F) sequences.

developed progressive disorientation, agnosia, anomia, cortical blindness, and incontinence. He was ultimately admitted to hospice care and died 2 years after initial diagnosis. He never developed evidence of neuropathy.

DISCUSSION

Based on the presentation of progressive, subacute cognitive decline in the context of treatment for multiple myeloma, the differential diagnosis initially included chemotherapy-induced leukoencephalopathy, meningoencephalitis, endocrine-metabolic derangements, genetic causes of leukodystrophy, and CNS involvement of multiple myeloma.

X-linked adrenoleukodystrophy is an inherited disorder where the mutated gene encoding the protein ATP-binding cassette, subfamily D, member 1 (ABCD1) results in defective transport of VLCFAs from the cytoplasm into the peroxisome. Altered peroxisomal metabolism causes accumulation of saturated VLCFAs in various tissues, primarily the adrenal cortex and the nervous system.^{1,2} One of the rarest phenotypes is the adult-onset cerebral form, with a relative frequency of 1%–3%.² This typically presents with subacute cognitive decline or psychiatric disturbances. In one survey, 17% of patients presented exclusively with psychiatric symptoms, and in patients older than 21, 5 of 6 presented with initial psychiatric symptoms.³

Because the patient exhibited mild cognitive changes prior to initiation of chemotherapy, one considers the possibility that chemotherapy provoked a more marked decompensation. However, we are not aware of reports of leukoencephalopathy with this chemotherapy regimen. Bortezomib is a proteasome inhibitor, and lenalidomide inhibits interleukin-6, activates apoptotic pathways, and modifies natural killer cell function.⁴ While neither of these agents have yet to be implicated in causing leukodystrophy, bortezomib has been associated with posterior reversible leukoencephalopathy (PRES) in a few case reports, and a phase II study reported confusion and aphasia as potential serious adverse events.⁵ Importantly, chemotherapy-induced leukodystrophy often occurs months after initiation of treatment, unlike our patient's symptom progression. As adrenoleukodystrophy is caused by flawed peroxisomal metabolism and bortezomib

and lenalidomide are not known to interfere with this biochemical pathway, it is unclear if there was accumulation of chemotherapy metabolites expediting this patient's decline.

Additional contributors to this patient's worsening mentation were also considered. Chronic infectious etiologies were excluded by the negative CSF findings. Direct CNS involvement of multiple myeloma, defined as the presence of myeloma cells in the CSF, is rare and can present with diffuse cerebral dysfunction, cranial nerve palsies, and radiculopathies; CSF cytology was negative for myeloma cells.^{6,7}

It is important to recall that X-linked adrenoleukodystrophy may present in adulthood, manifesting merely as gradual-onset psychiatric disturbances or cognitive decline.

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