Dear Editor,

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare cause of adult-onset leukodystrophy. It is most often inherited in an autosomal dominant mode and was previously known as hereditary leukoencephalopathy with axonal spheroids. Typically, patients in their middle age present with progressive cognitive decline and behavioral changes with pyramidal or extrapyramidal signs. A high index of suspicion is required to make an early diagnosis. We describe a middle-aged Indian male with ALSP. A 53-year-old army veteran with a history of systemic hypertension presented with long-standing and progressive cognitive decline. He had developed progressive memory impairment, wandering, aggressive behavior, difficulty walking on uneven ground, burning sensation in the feet, bowel-bladder abnormalities, and new onset gustatory facial hyperhidrosis for the past five years. As he was unable to carry out his duties, he resigned and pursued another career. However, he was unable to cope with the demands of his new job and had to resign again. He had six healthy brothers and there were no similar family complaints.

On examination, he had spasticity of the left leg with sluggish deep tendon reflexes, impairment of vibration sense below the ankles, impaired visuospatial and constructional abilities, and acalculia. A detailed neurocognitive evaluation revealed impaired cognition (MMSE = 22, MOCA = 56). Given the early-onset cognitive and behavioral changes and a multisystem involvement (corticospinal, autonomic, and subclinical peripheral neuropathy), in our patient, the following differential diagnoses were considered: multiple system atrophy, primary CNS vasculitis, and adult-onset leukodystrophies. Among, the leukodystrophies with autonomic features, AD adult-onset leukodystrophy (ADLD) and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) were considered as most likely.

He presented to us with an MRI which showed multiple scattered white matter lesions (predominantly fronto-parietal), that involved the subcortical U-fibers and did not demonstrate diffusion restriction or contrast enhancement. MRI also demonstrated radial dilated Virchow-Robin spaces in the subcortical white matter, extending up into the gyri [Figure 1]. MR angiogram was normal. He was initially evaluated for stroke with a battery of investigations including a complete blood picture, ESR, RFT, LFT, TFT, Hba1c, Serum B12 levels, and Vitamin D levels, SARS-CoV2 RTPCR, and a CSF study (total counts- 3, low CSF glucose- 39, protein- 32 mg), serology – HIV, HCV, HbsAg and VDRL, all of which were normal. An EEG was normal; however, nerve conduction studies showed an axonal sensory-motor neuropathy in the

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Table 1: Diagnostic features of ALSP suggested by Konno et al.[1]

| Core features                  |  |  |
|-------------------------------|  |  |
| Age at onset ≤60 years        |  |  |
| >2 findings of the following clinical signs and symptoms |  |  |
| Cognitive impairment or psychiatric symptoms |  |  |
| Pyramidal signs               |  |  |
| Parkinsonism                  |  |  |
| Epilepsy                      |  |  |
| Autosomal dominant inheritance or sporadic occurrence |  |  |
| Neuroimaging findings         |  |  |
| Bilateral cerebral white matter lesions |  |  |
| Thinning of the corpus callosum |  |  |
| Other causes of leukoencephalopathy including vascular dementia, multiple sclerosis, or leukodystrophy have been excluded |  |  |

Exclusionary findings

| Age at onset ≤10 years |  |  |
| >2 stroke-like episodes |  |  |
| Prominent peripheral neuropathy |  |  |

Supportive findings

| Clinical or neuropsychological tests demonstrating frontal lobe dysfunction |  |  |
| Rapidly progressive course with patients becoming bedridden within 5 years of onset |  |  |
| Stepping stone appearance in the frontal pericallosal regions on CT scans. |  |  |
| Neuropathologic findings compatible with ALSP |  |  |
| Definite ALSP: Fulfills core features 1-3, and 4a and has a confirmed CSF1R mutation |  |  |
| Probable ALSP: Fulfills core features 1-5, but genetic tests have not been performed |  |  |
| Possible ALSP: Fulfills core features 2a, 3, and 4a, but genetic tests have not been performed |  |  |
lower limbs. Visual evoked potentials (VEP) were prolonged in the left eye. A repeat brain MRI showed no change from his previous MRI. Fundus examination was normal.

Clinicoradiologically, it can be difficult to distinguish between patients with severe acquired small vessel disease and adult genetic leukodystrophies. However additional features such as movement disorders (parkinsonism or chorea), urinary symptoms, peripheral demyelinating neuropathy, or adrenal failure may suggest genetic conditions.

Clinical exome sequencing (CES) was performed to differentiate between adult-onset leukodystrophies. CES showed a novel heterozygous 5' splice variation in intron 9 of the CSF1R gene (chr5:g.150070181C>T; Depth: 231×) that affects the invariant GT donor splice site of exon 9 (c.131+1G>A; ENST00000286301.7), confirming the diagnosis of colony-stimulating factor 1 receptor (CSF1R) related ALSP.

Our diagnosis of ALSP fit into the diagnostic criteria for definite ALSP published by Konno[1] [Table 1]. Although our patient had a subclinical neuropathy (detected on NCV), prominent peripheral neuropathy (which is an exclusionary criterion) was absent. Many other white matter lesions can mimic ALSP [Table 2].

As hematopoietic stem cell transplantation (HSCT) is useful in ALSP by correcting CSF1R loss-of-function in microglia, he is undergoing evaluation for HSCT.[2]

ALSP is an autosomal dominant leukodystrophy that is associated with a heterozygous mutation in the colony-stimulating factor 1 receptor (CSF1R) gene. Although it is common in Japan, cases in India are rare.[3,4] Patients with ALSP have a heterogeneous clinical presentation. The most common presenting features include progressive neurological decline (personality changes, cognitive decline, memory decline, and depression). Motor impairment includes pyramidal and extrapyramidal signs. As the disease progresses, dementia supervenes. Most often it is inherited in an autosomal dominant mode, although sporadic causes are described.

In ALSP, brain MRI findings include deep white matter lesions in the frontal and parietal white matter, deep subcortical and periventricular areas. These are usually T2 hyperintense and T1 hypointense on T1-weighted images. The white matter signals spare the U-fibers but may involve the pyramidal tracts.[5] Unlike other leukodystrophies, scattered foci of restricted diffusion are present in the white matter (diffusion dots), which can mimic the appearance of CNS vasculitis.[6]

### Table 2: Adult-onset white matter diseases

| Diseases                        | Clinical features             | Differentiating feature from ALSP                           |
|---------------------------------|-------------------------------|------------------------------------------------------------|
| Adult-onset AD leukodystrophy   | Cognition impaired            | Early ANS dysfunction                                      |
| LMNB1 gene                      | Pyramidal and cerebellar signs| Periventricular rim on MRI                                |
| Alexander disease (AD)          | Bulbar/pseudobulbar signs     | Cognition normal                                           |
| GFAP gene                       | Ataxia                        | Infratentorial atrophy                                     |
| CADASIL                         | Frontal lobe syndrome         | Stroke-like presentation                                   |
| NOTCH3 gene                     | White matter lesions (WML)    | Multiple infarcts and white matter lesions (WML) in temporal region |
| Fronto-temporal dementia        | Pyramidal and extrapyramidal signs | Frontal and temporal atrophy                             |
| C9orf72 gene/GRN related        | Frontal lobe syndrome         | Few WML                                                    |
| Early onset Alzheimer’s disease | Executive dysfunction         | Episodic memory loss                                       |
| APP gene/PSEN1,2 gene           | Personality changes           | Less WML                                                   |
| Nasu-Hakola disease             | Similar onset age             |                                                            |
| Vanishing white matter disease  | Insidious personality changes | Feet/wrist tenderness                                      |
| Adult type metachromatic leukodystrophy | Frontal lobe syndrome | Poly cystic lesions                                       |
| CADASIL                         | Motor abnormality, dementia, progress to vegetative state | Pathological fractures |
| NOTCH3 gene                     | Cerebellar ataxia             | U-fibers partially affected on MRI                        |
| Adult-onset Krabbe disease      | Executive and personality changes | Peripher neuropathy                                      |
| X-linked adrenoleukodystrophy   | Memory decline                | White matter lesions including cerebellum                 |
| MELAS/MNGIE                     | Pyramidal signs               | Tigroid appearance                                         |
| Primary progressive multiple sclerosis | Seizures                | Peripheral neuropathy                                      |
| Susac syndrome                  | Cognitive and behaviour changes | WML in brain stem, cerebellum, occipital region          |

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Although early lesions are patchy, they become confluent with time. The presence of non-enhancing white matter lesions with persistent diffusion restriction and corpus callosum thinning differentiates ALSP from other causes of acquired demyelination. Infra-tentorial areas are also spared, differentiating ALSP from hypertensive small vessel white matter ischemia. Although our patient did not show diffusion restriction, there were extensive linear Virchow-Robin spaces resembling a tigroid pattern.

CT scans may show symmetrically aligned calcifications along the upper edges of the lateral ventricles, that is, a “stepping stone appearance”.[7]

Until now, the management of ALSP was largely supportive. However, HSCT has been recently shown to be useful in CSF1R-associated ALSP.[2]

CNS microglia are highly dependent on CSF1R signaling. Decreased signaling via CSF1R leads to the rapid apoptosis of microglia. However, microglial numbers can be replenished if CSF1R signaling is reestablished. CSF1R genetic mutations are microgliopathies associated with loss of function mutations affecting the tyrosine kinase domain of the CSF1R gene.

The majority of ALSP cases exhibit autosomal-dominant inheritance and a mean age of onset of symptoms in the 5th decade (approximately, an average of 43 years). Our patient had a sporadic ALSP that presented in his 5th decade. Sporadic cases are due to genetic mosaicism, incomplete penetrance, or de novo mutations. If left untreated, ALSP runs an inexorably fatal course within six to seven years from the onset of illness. Hence, HSCT has been offered as a treatment option. Our patient with ALSP showed some unusual features such as a subclinical neuropathy, involvement of the U-fibers in the frontal cortex, prominent linear Virchow-Robin spaces, and absent diffusion restricted lesions on MRI.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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