Dear Editor,

A 46-year-old woman with a past medical history of asthma, migraine headache, obstructive sleep apnea, angle-closure glaucoma, silent sinus syndrome, and Axenfeld-Rieger syndrome (ARS) secondary to a FOXC1 mutation presented to the outpatient clinic with visual changes, worsening eye pain, migraine, vertigo, and paresthesia in bilateral lower extremities. She reported that migraine headaches occurred three times a week with intermittent dizziness for the past three years and pins and needles sensation in bilateral lower extremities for the past 18 months. At the time of presentation, active medical treatment included amitriptyline, brimonidine, latanoprost, and timolol. She denied any weight changes, dental or swallowing difficulties, and heat/cold intolerance. Neurological examination was only remarkable for diminished sensation to pinprick touch in the distal right lower extremity, mainly in the foot and lateral shin area. Magnetic resonance imaging (MRI) revealed multiple foci scattered in the supratentorial white matter involving the periventricular region, corona radiata, and subcortical region (Figure 1). No enhancing lesions were viewed on post-contrast imaging to suggest an active inflammatory process.

Cerebrospinal fluid (CSF) was unremarkable for glucose, protein, and oligoclonal bands. Her rheumatological panel was significant only for an erythrocyte sedimentation rate of 28 mm/hr. Her secondary neuropathy laboratory findings were unremarkable as well. Nerve conduction velocity studies did not show evidence of large fiber polyneuropathy except evidence of right sided L5 radiculopathy; however, small fiber neuropathy could not be ruled out. No further changes to the management plan were made and imaging findings were attributed to its rare mimicker ARS.

ARS is a rare autosomal dominant, genetically heterogeneous condition, with pathogenesis attributable to mutations in the PITX2 and FOXC1 genes. There is limited literature on subcortical white matter lesions on MRI in patients with ARS. This rare disease can manifest with many ocular and systemic abnormalities, including neurological symptoms. Neuropsychiatric symptoms, leukoencephalopathy, and non-specific T2 lesions attributed to microvascular disease are reported in ARS (1). At least one report in the literature has documented leukoencephalopathy in the setting of ARS resulting from a mutation in FOXC1. FOXC1 mutations cause impaired microvasculature stability resulting in cerebral small vessel disease (CSVD) (2). This is likely to be attributed to FOXC1 regulating platelet-derived growth factor, of which signaling allows for regulation of neural crest recruitment and mural cell migration in the stability of developing vasculature. CSVD has been identified in 1-year-old infants with inhibited FOXC1 function. MRI analysis has demonstrated white matter hyperintensities and lacunar infarctions in patients with missense, non-sense, as well as segmental duplication of and deletion in FOXC1 gene. A similar result was identified in PITX2, a neural crest-expressed transcription factor. Limited studies have documented PITX2’s interaction with FOXC1, and results suggest that PITX2 may play a role in gene activation of FOXC1. Further research is necessary to determine the extent of the

Keywords: Axenfeld-Reiger syndrome, multiple sclerosis, white matter changes, mimickers

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interaction and its effect on vascular basement membrane security, potentiating a high stroke risk in patients (3). Non-specific T2 lesions on brain MRI are common mimickers of multiple sclerosis (MS), and these patients are often misdiagnosed as having MS. In one study, up to 20% of the patients referred to a tertiary MS clinic were misdiagnosed (4). Common causes of T2 lesions in MS are demyelination of medullary venules close to the ventricular walls and ischemic microvascular lesions. These lesions’ number, distribution, and clinical context are vital in determining their significance. Multiple vascular and inflammatory disorders are often mistaken for MS due to indistinguishable lesions affecting distinct areas. One such example is systemic lupus erythematosus which can produce multiple T2 intensities in the periventricular white matter but are differentiated by their propensity to choose grey matter and cause systemic clinical features (5). There is no biomarker for MS, and often the diagnosis is made based on clinical

Figure 1. Cranial T2- and FLAIR-weighted axial and sagittal MRI images of a patient with ARS. Multiple T2 lesions are seen predominantly in subcortical white matter

ARS: Axenfeld-Rieger syndrome, MRI: Magnetic resonance imaging
presentation, MRI findings consistent with demyelination, and supportive CSF findings in exceptional cases. T2 lesions in MS often have typical morphology and are in distinct locations such as the periventricular and juxtacortical regions. Our patient also has a history of migraine headaches commonly associated with non-specific T2 lesions in the brain. It is unclear if migraine headaches are related to ARS or not. However, the molecular association of FOXC1 mutation with CSVD suggests these two entities are related to the ARS spectrum rather than unrelated findings. To improve comprehensive patient care, more radiographic images of patients with ARS should be collected to further guide the management.

The CSVD in ARS can radiologically mimic demyelination. MS is primarily a clinical diagnosis supported by central nervous system imaging findings consistent with T2/FLAIR hyperintensities involving the juxtacortical, periventricular, infratentorial, or spinal cord, and by the presence of oligoclonal bands in CSF. However, clinicians should always keep in mind the possibility of mimickers of MS in patients with underlying vascular and inflammatory disorders and genetic conditions due to impaired microvasculature stability resulting in CSVD.

**Ethics**

**Informed Consent:** Informed consent was obtained from the patient.

**Peer-review:** Externally and internally peer-reviewed.

**Authorship Contributions**


**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

**References**