



Case report

Delayed-Onset multiphasic demyelinating lesions after high dose radiofrequency electromagnetic field exposure: A multiple sclerosis (MS) mimic

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1. Introduction

The 2017 McDonald's criteria suggest a diagnosis of multiple sclerosis (MS) when clinical symptoms and/or neuroimaging favor dissemination in space and time. However, its specificity in distinguishing MS from other etiologies with similar presentations, such as neurosarcoidosis, acute disseminated encephalomyelitis, cerebrovascular disease, migraines, paraneoplastic syndromes, or radiation injury, remains low (Brownlee et al., 2017). Of these alternate diagnoses, radiation injury causing white matter lesions from accidental non-therapeutic whole-brain radiation is sparsely described in literature, and remains a leading cause of misdiagnosis and delayed treatments (Andrews et al., 2017). We present multiple years of clinical, laboratory and neuroimaging findings of one such case of clinical manifestation of whole brain radiation to aid neurologists and other practitioners to better identify and manage this disorder.

2. Methods

This is an investigational case report utilizing retrospective data from electronic medical records. No identifiable patient information is shared to maintain patient privacy and comply with the University of California research guidelines.

3. Results

Our patient is a 46-year-old Caucasian engineer with no significant past medical history. In 2011, he was exposed to prolonged high levels of radiofrequency electromagnetic field (RF-EMF) radiation during a technical malfunction at a cell phone tower. Unfortunately, a radiation monitor was not worn during the incident but company guidelines suggested that only 6 min of exposure was safe. In contrast, the patient remained directly in front of 15 active transmitters for at least 2 h. Immediately post exposure, he suffered cutaneous burns to his face, neck, and back, and developed eye, joint, muscle and stomach pain. An

MRI brain with and without contrast at the time was unremarkable and his symptoms resolved completely after a few days of supportive treatment. Unfortunately, in 2016, our patient started to have right hand weakness and numbness. Initial outpatient MRI of the cervical spine revealed mild-to-moderate spinal stenosis. He underwent an anterior cervical discectomy and fusion of C4-C7 the same year, though his symptoms only partially resolved. In 2017, he re-presented to the primary care clinic with new-onset left arm and hand weakness. Outpatient workup with an electromyogram revealed left ulnar neuropathy. He was then recommended to have an ulnar transposition, which he underwent successfully but with no symptomatic relief. Given the persistence of his symptoms, an MRI brain was ordered and he was referred to a Neurologist. Compared to the 2011 MRI brain which had been unremarkable, the T2 fluid attenuated inversion recovery sequence (T2 FLAIR) on this 2017 MRI brain showed multiple oval-shaped hyperintense lesions involving the juxtacortical, periventricular and deep white matter regions without restricted diffusion or enhancement (Fig. 1).

He was first seen by a Neurologist in mid-2018 when neurological examination revealed right hand and left forearm and hand weakness and decreased sensation, consistent with the symptoms described above. However, the patient reported recent worsening of his symptoms and a repeat MRI brain and cervical spine were ordered. Compared to prior scans, the 2018 MRI brain showed stable lesions but the MRI cervical spine showed a new T2 hyperintense lesion (Fig. 2). Although post-radiation white matter injury was in the differential, the etiology of this new inflammation was unclear and a thorough workup was undertaken to rule out other etiologies. Specifically, our investigation revealed normal levels of ANA, SSA/SSB, ANCA (P-ANCA and C-ANCA), antismyeloperoxidase, HIV, ACE, and CRP. Lumbar puncture revealed normal glucose, protein and cell counts with no oligoclonal bands and no growth on bacterial, fungal and viral cultures. Despite this, the patient did meet McDonald's criteria for MS and was offered a trial of first-line MS medications, but he refused therapy at the time.

Subsequently the patient re-presented to our clinic in 2019 with

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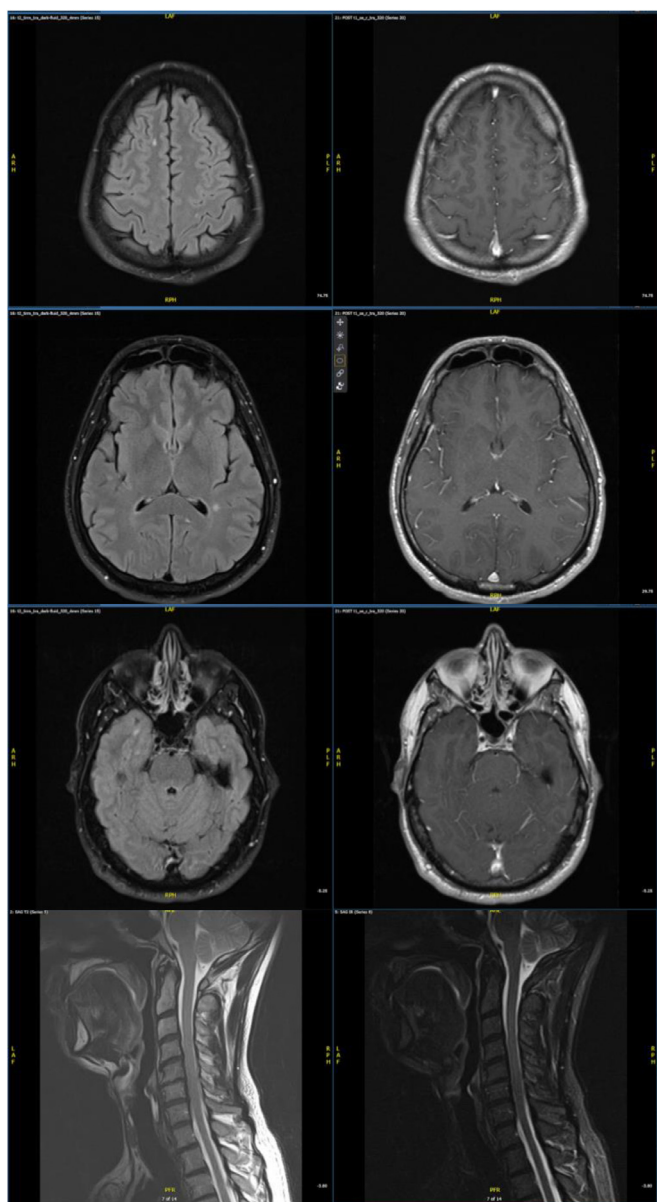


Fig. 1. A 2017 MRI brain and cervical spine from a 46 year old male with remote accidental radiation exposure and history of right hand weakness and numbness who now presents with new-onset left arm and hand weakness. On the left are axial images from the T2 fluid attenuated inversion recovery sequence, and on the right are corresponding axial images from the post-contrast T1 sequence. The scan shows multiple oval-shaped hyperintense lesions involving the juxtacortical, periventricular and deep white matter regions without restricted diffusion or enhancement.

complaints of burning in his stomach, leg weakness, decreased mental clarity, difficulty sleeping and excessive irritability. A repeat MRI brain demonstrated an interval increase in the number of T2 FLAIR hyperintense lesions in the juxtacortical, periventricular and other areas without any enhancement (Fig. 3). An interval pan-CT scan now showed nodules in the kidney and bilateral lungs consistent with possible radiation-induced tumors. A paraneoplastic panel was analyzed at Immco diagnostics and reported as negative for any antibodies. The patient again refused a trial of therapies targeted against demyelination, opting instead of continued supportive treatment with hydrocodone only.

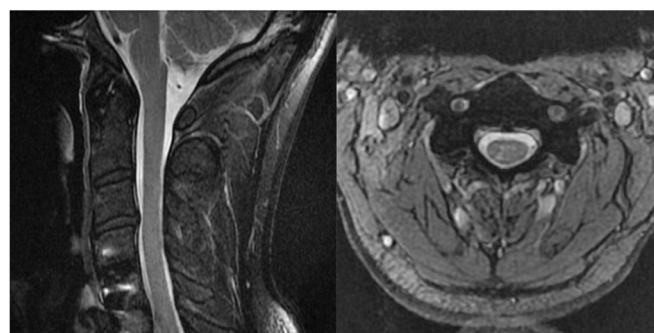


Fig. 2. Interval Development of Cervical Spine Demyelination. Follow-up 2018 MRI brain and cervical spine from a 46 year old male with remote accidental radiation exposure who now presents with worsening of right hand and left arm and hand weakness and numbness. On the left is a T2 fat suppressed sagittal image along with the corresponding T2 axial image.

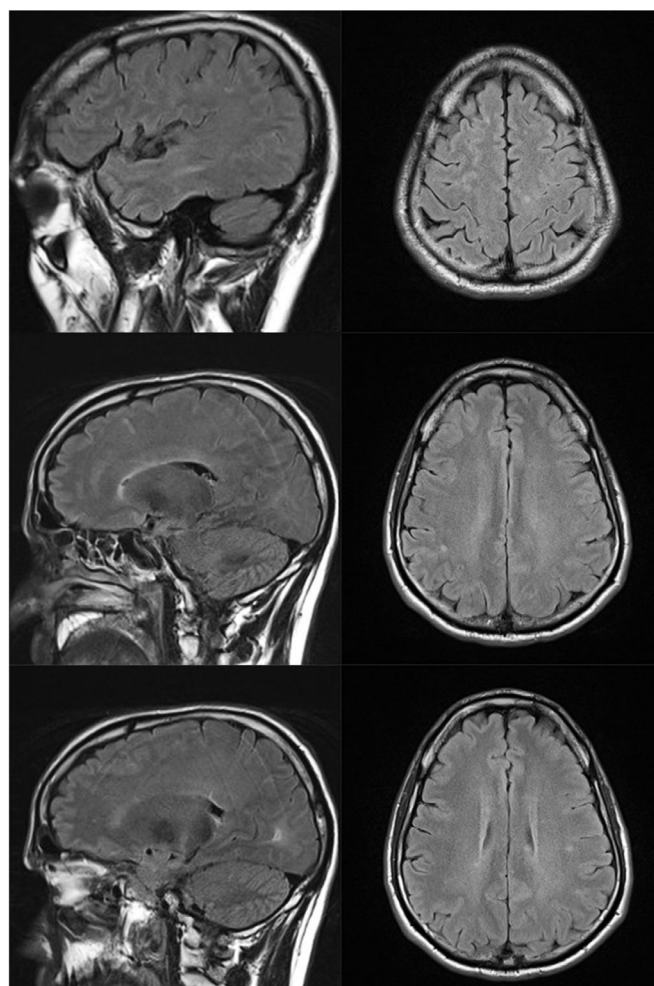


Fig. 3. Sagittal and Axial FLAIR images from a follow-up 2019 MRI brain showing juxtacortical and periventricular T2 hyperintense lesions with characteristics compatible with a diagnosis of Multiple Sclerosis.

4. Discussion

This case report presents a patient who clinically had more than three isolated loss-of-function events and radiologically had multiple demyelinating juxtacortical, periventricular, and spinal cord lesions from different time periods, thus meeting the 2017 McDonald's criteria for a diagnosis of MS. However, his history of accidental non-

therapeutic whole-brain radiofrequency electromagnetic field exposure, associated symptoms of fatigue, mood changes, cognitive dysfunction, and negative findings on blood and cerebrospinal fluid studies suggests a possible alternate diagnosis: sequential demyelination as a complication of remote radiation injury (Mehta et al., 2017). This is further supported by his subsequent development of kidney and lung masses resembling radiation-induced tumors. Paraneoplastic processes were also in the differential, though a thorough testing of antibodies was entirely negative.

Radiation induced brain injury has been studied more extensively in cancer populations, the majority of whom presented with a syndrome including fatigue, mood changes, cognitive dysfunction, ataxia and urinary incontinence. MRI scans of these patients showed early signs of sequential demyelination with potential irreversible effects, though long-term follow-up data over 6 months is as yet inconclusive. Demyelinating lesions are associated with multiple pathophysiological mechanisms, including induction of perivascular cellular infiltrates, alterations in myelin composition, damage to the blood brain barrier, and oligodendrocyte injury. In a study exposing non-human primates to radiation, those with white matter degeneration and necrosis were found to have perivascular edema, abnormal angiogenesis and perivascular extracellular matrix deposition, suggesting a cerebrovascular mechanism (Andrews et al., 2017). However, in a study exposing mice to extended RF-EMF, the cortex displayed direct damage to the myelin sheath with relative sparing of other structures (Kim et al., 2017). In a review by Redmayne and Johansson, 2014, they note that preliminary evidence suggests RF-EMF exposure increases the risk for MS.

Most of the treatment for radiation demyelination and necrosis also comes from the cancer literature. Therapeutic radiation of the brain can induce acute or chronic neurological disorders, with pathologic imaging findings and symptoms ranging from asymptomatic to very symptomatic, including impairment of mental function, such as personality changes, memory deficits, and confusion. The extent of demyelination from radiation depends on multiple factors, including radiation dose, fractionation methods, or if focal areas or the whole brain was affected.

Corticosteroids are a mainstay in treatment for radiation induced demyelination and can reduce cytokine responses, dampen permeability of the blood brain barrier, and lessen edema. Treatment with corticosteroids is associated with resolution of neurological deficits in patients with radiation necrosis. Due to the many adverse side effects of long-term steroid use, other treatments are now used for radiation induced demyelination. Other possible therapeutic options include hyperbaric oxygen therapy and vascular endothelial growth factor (VEGF) inhibitors such as Bevacizumab (Mehta et al., 2017). Because treatments that have been explored have been intended for the management of radiation necrosis, they may not be relevant to the treatment of multiphasic demyelination observed in this case or MS in general. Additionally, it is unclear if and to what extent these patients would benefit from disease-modifying MS treatments.

In summary, this case illustrates that high levels RF-EMF exposure can either increase risk for the development of MS or induce a condition that mimics the presentation of multiple sclerosis both clinically and radiologically. Thus, extreme RF-EMF radiation should be kept in the differential diagnosis when taking a thorough neurological history. Despite case reports that corticosteroids may be effective in the prevention of sequential demyelination in oncological patients who received therapeutic whole brain radiation, our patient refused to try any therapies beyond pain control and we are unable to comment on their efficacy in this case. We encourage further investigations into the true incidence and mechanism of this disorder, with hopes that tailored therapies may soon become available for patients like ours.

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CRediT authorship contribution statement

Sophia M Raefsky: Conceptualization, Investigation, Writing - original draft. **Amit Chaudhari:** Conceptualization, Investigation, Visualization. **Michael Y. Sy:** Conceptualization, Investigation, Visualization, Writing - review & editing.

Declaration of Competing Interest

Sophia Raefsky has no relevant disclosures or conflict of interest. Amit Chaudhari was involved in clinical care of described case but has no other relevant disclosures or conflict of interest. Michael Sy was involved in clinical care of described case but has no other relevant disclosures or conflict of interests.

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