A Case of Levamisole Induced Multifocal Inflammatory Leukoencephalopathy and Secondary Nocardia Veterana Brain Abscess

Sir,

Levamisole is a synthetic antihelminthic belonging to the class of imidazothiazole derivatives, possessing potent immunomodulatory activity. It has been used as an adjunct for chemotherapy, for nephrotic syndrome and as a multifaceted drug in Dermatological conditions such as alopecia. Multifocal inflammatory leukoencephalopathy (MIL) is a demyelinating disorder of the central nervous system rarely occurring as an idiosyncratic side effect of Levamisole.[1,2] Early diagnosis of MIL and discontinuation of Levamisole is essential which may amount to a favorable outcome.[3-5] The management also encompasses the use of steroids, plasmapheresis, intravenous immunoglobulins, and immunosuppressants. Infections with atypical organisms may occur following immunomodulatory treatment. Nocardia veterana has been very rarely known to cause brain abscesses.[6]

A diabetic 57-year-old lady presented to us with progressive drowsiness for three days. She had associated irrelevant talk, slurred speech, and ataxia. She had been on oral Prednisolone, Minoxidil, and Levamisole 150 mg twice daily for Alopecia for the last 2 months and she had received intralesional steroids to the scalp one month ago.

On clinical examination, she had a Glasgow Coma Scale of 9/15, was responding to verbal stimuli and moving all limbs. Plantars were equivocal and she had no neck stiffness. She was admitted with a provisional diagnosis of an encephalopathy. Workup showed mild leucocytosis and elevated C-Reactive Protein of 12 mg/dl (<3 mg/dl). Magnetic Resonance Imaging (MRI) of Brain with contrast showed multiple lesions in both hemispheres especially around the periventricular region suggestive of multiple bilateral demyelinating lesions [Figure 1].

An autoimmune workup including ANA, pANCA, cANCA, anti-cardiolipin, and lupus anticoagulant antibodies was negative. Serology for HIV, Hepatitis B and hepatitis C were negative. CSF study revealed only 4 lymphocytes, normal protein, and sugar. CSF protein electrophoresis did not reveal any abnormal bands in the gamma globulin region nor any oligoclonal bands. CSF auto-immune panel for consisting of Neuromyelitis Optica spectrum disorders (NMOSD) autoantibodies to Myelin Oligodendrocyte Glycoprotein (MOG) and Neuromyelitis Optica (NMO/Aqp4) was negative. CSF paraneoplastic panel was also negative. CSF Meningo-encephalitis multiplex PCR panel was negative. A diagnosis of autoimmune demyelination with Vasculitis, possibly triggered off by Levamisole was made. She was started on intravenous steroids along with intravenous Immunoglobulin but did not show any clinical improvement.

Repeat MRI showed fresh lesions in both cerebral hemispheres, cerebellum, and cerebellar peduncles. MR Angiogram revealed beading in the peripheral small vessels. A Digital Subtraction Angiography was done vasculitis confirmed [Figure 2]. A CT Thorax and abdomen with contrast was done to look for any underlying malignancy which may have caused vasculitis and it was normal. Because there was no response to intravenous immunoglobulin, she was given a course of Cyclophosphamide for the suspected autoimmune process with continuation of IV Steroids. However, repeat MRI done did not show any regression, and there was development of two new lesions.

Given the persisting MIL, she was given a course of Rituximab followed up 2 weeks later with a second dose, after which she showed clinical response. She occasionally opened her eyes spontaneously but there was still no eye contact. Roving eye movements were present and there were no convulsions. She responded semi purposefully to stimuli and plantars became flexor.

Repeat MRI after the course of Rituximab showed a regression of the lesions and there were no new lesions. After 40 days of hospital stay, she was then shifted to another center for rehabilitation.

Two months later, she was re-admitted with worsening neurological status. A repeat MRI brain with MR angiogram was done which showed an abscess [Figure 3]. A Craniotomy and decompression with biopsy via left frontal craniotomy was performed. AFB smear, GeneXpert, and Mycobacterial cultures were negative. Pan Bacterial and Pan fungal Real-Time PCR

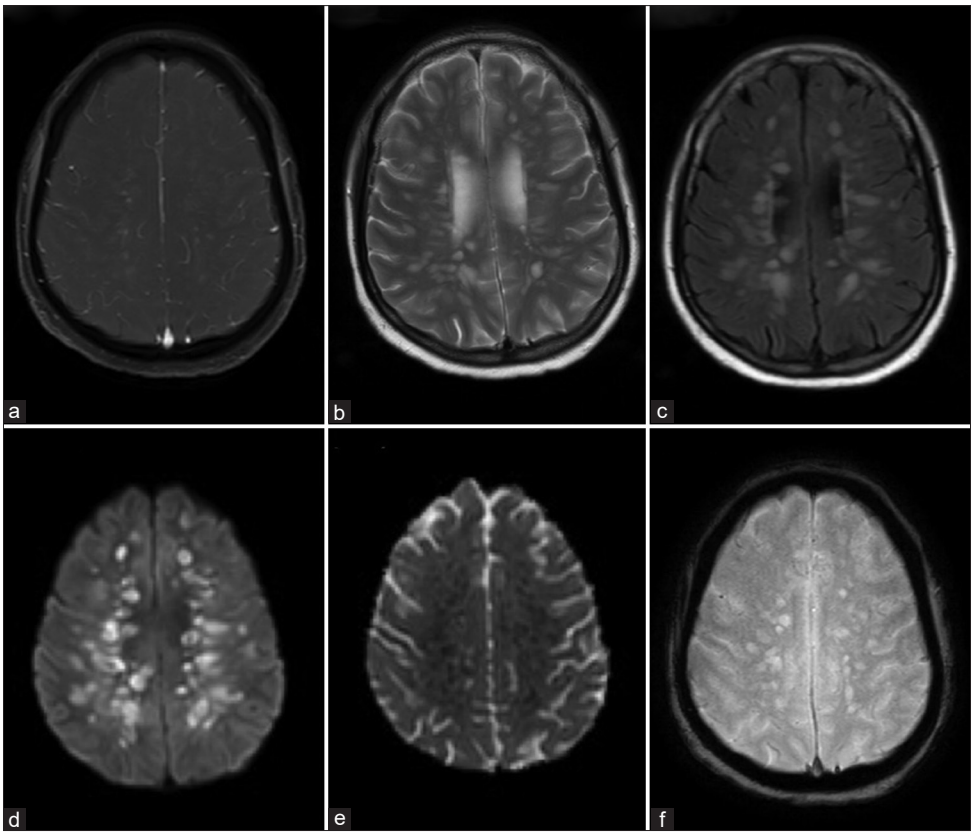

Figure 1: Brain parenchymal bilateral periventricular lesions suggestive of demyelination seen on (a) Axial post contrast section (b) Axial T2 weighted section (c) Axial Flair Section (d) Axial Diffusion weighted section (e) Axial apparent diffusion coefficient section (f) Axial Gradient echo sequences section

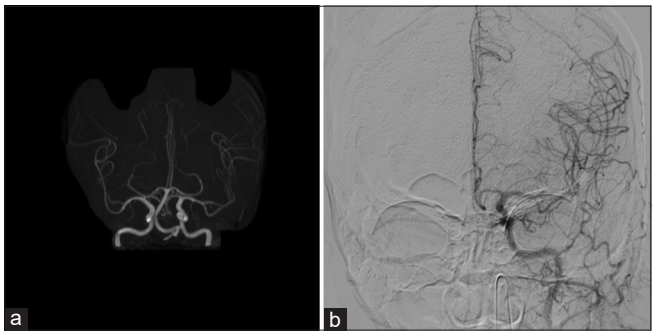

Figure 2: (a) Magnetic Resonance Angiography showing beaded appearance suggestive of vasculitis (b) Digital Subtraction Angiography showing beaded appearance confirming the same

done detected bacterial 16sRNA suggestive of bacteria in the specimen. The biopsy sample grew Nocardia species on Vitek2. This was confirmed by Matrix-assisted laser desorption ionization-Time of Flight Mass spectrometry (MALDI-TOF) and species was identified to be Nocardia Veterana. She was treated with Meropenem and Linezolid as per culture and sensitivity for 2 weeks and stepped down to Cotrimoxazole and Amoxicillin-Clavulanate for a total of 12 months. A Chest Xray during this admission was normal.

A repeat computed tomography of the brain after the surgery confirmed good decompression of the abscess cavity. Her immunomodulatory treatment was changed to Mycophenolate mofetil, antibiotics continued, and steroids tapered. The patient made a complete clinical recovery on follow up with no residual neurological deficits.

This case proved to be a clinical conundrum with two rare pathologies sequentially intertwined in a single patient; Levamisole induced multifocal inflammatory leukoencephalopathy (MIL) complicated by secondary infection with Nocardia Veterana. Demyelinating diseases are neuropathological entities most frequently observed in the central nervous system with preferential involvement of the major white matter tracts in a periventricular distribution.

Nocardia species are gram-positive, non-motile aerobic actinomycetes that are ubiquitous environmental saprophytes. They cause a varied and broad spectrum of suppurative and granulomatous infections. While Nocardia can cause disease in an immunocompetent host, they are often considered opportunistic pathogens, causing disease in settings of compromised immunity. N. veterena, a component of the Nocardia Nova complex, is a newly described species whose pathogenicity is poorly described and is mostly associated with pulmonary pathologies.[6] Only a handful of cases associated with infection of the central nervous system caused by Nocardia Veterana have been reported in the literature.[7]

This case serves to highlight that, although rare, we should

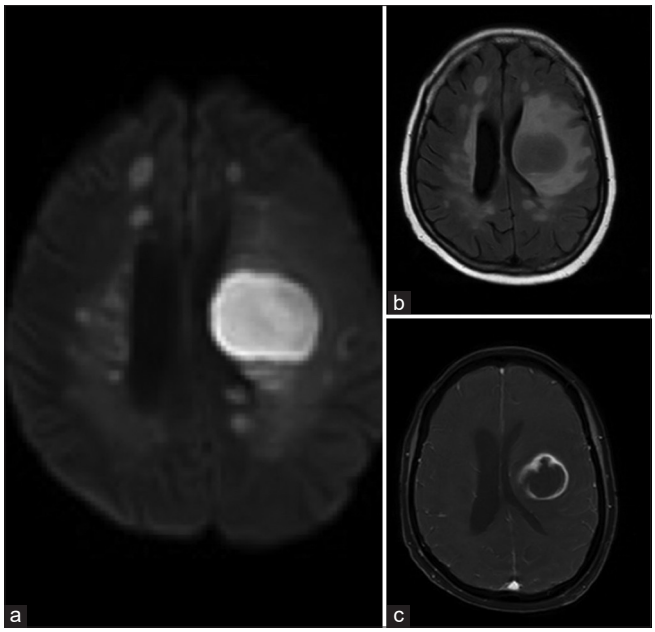

Figure 3: Brain abscess seen on (a) Axial Diffusion weighted section (b) Axial Flair section (c) Axial post contrast section

be watchful for dreaded complications of Levamisole. Early diagnosis of MIL and discontinuation of Levamisole may amount to a favorable outcome. We wish to reiterate that a detailed history is of paramount importance for diagnosing levamisole-induced leukoencephalopathy and emphasize the need for a high degree of suspicion of an opportunistic infection in case of sudden deterioration of an immunocompromised patient.

Patients with depressed cell-mediated immunity like organ transplant recipients on pharmacological immunosuppression, low CD 4 T-Lymphocyte counts, hematological malignancies, and on long-term steroids or immunomodulator are at high risk for infection with the Nocardia species.[8] Diagnosis and treatment of nocardial brain abscesses are also challenging. Early diagnosis and surgical intervention are paramount for a good clinical outcome. Newer technology like MALDI-TOF can serve as a rapid and accurate identification tool which can augment sequencing in a clinical microbiology laboratory and improve clinical outcome by virtue of rapid turn around times.

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.

Reshma Ahammadunny, Balram Rathish, Mathew Abraham[1], Arun Wilson[2], Anup Warrier[2]

Departments of Internal Medicine, [1]Neurology, [2]Infectious Diseases, Aster Medcity, Kochi, India

Address for correspondence: Dr. Reshma Ahammadunny, Department of Internal Medicine, Aster Medcity, Kochi, India.
E-mail: drreshma.a@asterhospital.com

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