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Highly Active Relapsing-Remitting Multiple Sclerosis with Neurofibromatosis Type 1: Radiological Aspects and Therapeutic Challenges – Case Report

Marios Lemonaris[a] Kleopas A. Kleopa[b, c]

[a]Acute and General Medicine Department, Royal Infirmary of Edinburgh, NHS Scotland, Edinburgh, UK; [b]Department of Neuroscience, Nicosia, Cyprus; [c]Center for Multiple Sclerosis and Related Disorders, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

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Relapsing-remitting multiple sclerosis · Neurofibromatosis 1 · Natalizumab · Case report

Abstract
Introduction: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease which can rarely co-exist with neurofibromatosis 1 (NF1), a neurocutaneous inherited disorder that predisposes to oncogenesis. Patients who suffer from both conditions can be challenging cases for clinicians, as clinical symptoms and radiological findings may overlap, while MS immune-modifying treatments could further increase the risk of oncogenesis. ***Case Presentation:*** In this study, we describe the case of a 27-year-old woman who presented with signs and symptoms of optic neuritis and was then diagnosed with both MS and NF1. As the patient continued to experience MS relapses despite initial interferon-beta treatment, she was subsequently switched to natalizumab and responded well. ***Conclusion:*** This case illustrates how MRI lesion differentiation with the co-existence of MS and NF1 can be difficult due to overlaps in lesion characteristics, while treatment decisions can be challenging mainly due to scarce data on the oncogenic risk of MS immunomodulary therapies. Therefore, clinicians need to balance out the risk of malignancy development with the risk of progressive neurological disability when treating such patients.

Correspondence to:
Marios Lemonaris, marios.lemonaris@nhs.scot

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Introduction

Multiple sclerosis (MS) is an autoimmune-mediated inflammatory disease characterised by central nervous system (CNS) lesions which lead to demyelination, neurodegeneration, and gliosis [1]. The variation in lesion location gives rise to a spectrum of symptoms that include focal neurological deficits, vision impairment, bowel and urinary incontinence, and cognitive and physical disability or paralysis [1]. MS can be classified based on disease course with the most common being the relapsing-remitting form, defined by an episodic but progressive development of MS symptoms [1].

The hallmark of MS diagnosis (as outlined by the McDonald criteria) is damage to the CNS that is disseminated in space (DIS), where lesions in different CNS areas are identified through MRI, and dissemination in time, where there are clinically separate neurological episodes or attacks. DIS can be determined through the Magnetic Imaging in Multiple Sclerosis (MAGNIMS) criteria, where one or more lesions are found in at least two of the following CNS areas: periventricular, juxtacortical, infratentorial, and spinal cord [2]. The lesions are typically T2 hyperintense, while gadolinium enhancement indicates active lesions [1].

Even though MS is one of the commonest causes of neurological disability in the younger population, the aetiology and pathophysiology remain unclear [1]. However, current knowledge on MS has led to great advancements in disease-modifying treatments (DMTs) that have managed to reduce disease activity and progression. Notable examples include Interferon-beta and the monoclonal antibodies natalizumab and ocrelizumab [3].

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder resulting from missense, frameshift, or nonsense mutations or deletions in the *NF1* gene, which encodes the tumour-suppressor protein Neurofibromin [4]. The resulting tumorigenesis manifests as cutaneous nodules and plexiform neurofibromas, but also as malignancies including gliomas, astrocytomas, and breast cancer. Other features include café-au-lait spots which are usually the first feature to appear, freckling, Lisch nodules, and skeletal abnormalities [4]. Diagnosis of NF1 can be clinical, especially in the presence of a positive family history. NF1 predisposes patients to CNS tumours; however, it is also associated with other CNS alterations including epileptogenic lesions and vascular and CSF alterations such as hydrocephalus. An important MRI feature is the presence of focal abnormal signal intensities (FASI), which are classically T2-hyperintense non-enhancing lesions within the brain that can appear in up to 90% of NF1 patients. Initially, FASI are classically distributed in the brainstem, basal ganglia, thalamus, and cerebellum, while intensities in the cortex and hippocampi appear over time [5]. Currently, NF1 treatment is mainly symptomatic, as there is no definitive treatment available. Other treatment options include surgical excision for plexiform neurofibromas and early cancer screening, while potential options include oncolytic virotherapy and tumour suppressor gene therapy [4].

This case study reports the first case of MS and NF1 in Cyprus and focuses on the radiological aspects and the treatment challenges that exist in such patients. As the main aim of MS treatment is immunosuppression, this may raise the risk of malignancy which is even higher in the presence of a condition like NF1. The risk of malignancy development needs to be balanced with the risk of progressive neurological disability. Currently, there are no guidelines on the management of such patients, partly because of the rarity of their co-existence and the scarce data on the oncogenic risk of MS treatments.

Case Presentation

This case report concerns a 27-year-old female patient who was diagnosed with MS and NF1 after presenting with features suggestive of both conditions. Initially, the patient presented to the ophthalmologist with a 5-day history of unilateral vision loss and periocular pain during the first day only. The examination revealed vision loss and impaired colour saturation in the right eye, while dilated fundoscopy showed optic nerve pallor. An additional finding was the presence of Lisch nodules on the iris.

Initial MRI study of the brain and orbits revealed contrast-enhancing T2-hyperintense lesions in the right intracanalicular portion of the optic nerve, left internal capsule, along with a T2-hyperintense but T1-hypointense enhancing lesion in the right anterior temporal lobe (Fig. 1a–c). There were also T2-hyperintense lesions in the left centrum semiovale, corpus callosum, superior frontal lobe, and occipital horn of the lateral ventricle. Spinal cord MRI showed contrast-enhancing lesions in the C3 and T6/7 spinal cord levels, as well as multiple confluent lesions in the cervical and thoracic regions that included the conus medullaris. Finally, two subcutaneous neurofibromas were identified in the right occipital and temporal lobes, along with T2-hyperintense diffuse signal changes in the hippocampus.

Initial oncological evaluation indicated no evidence of optic glioma or other malignancy. The patient was then referred to a neurologist for further evaluation, as there was difficulty in clinically differentiating optic glioma due to NF1 and optic neuritis due to MS. On clinical examination, the patient was found to have more NF1 features including café-au-lait spots, axillary and groin freckling, as well as severe visual impairment on the right side.

Lumbar puncture and routine CSF analysis showed 10 WBC, normal glucose (58 mg/dL), and protein (28 mg/dL) levels. Flow cytometry analysis of CSF showed the majority of lymphocytes being mature CD3+ T cells with a CD4:CD8 ratio of 8.9, while 3.9% of lymphocytes were mature CD19+ B cells. A small population (0.1% of total cells) were CD38+ and CD138+ plasma cells. There was no suggestion of monoclonal lymphocytes. Further CSF and serum studies showed oligoclonal bands present in both, while the additional bands found in the CSF suggested intrathecal antibody production. CSF ACE level was within the normal range. Extensive serum studies for autoimmune and rheumatological markers and autoantibodies, complement levels, and serum protein electrophoresis were normal or negative. Ani-AQP4 and anti-MOG antibodies were also negative. CT scan of the chest, abdomen, and pelvis showed no evidence of malignancy. MRI abdomen was also normal.

The diagnosis of MS was made according to the McDonald criteria. Furthermore, as there was clinical and radiological evidence of NF1, the patient underwent genetic studies which confirmed a heterozygous de novo *NF1* mutation (c.1527+4_1527+7delAGTA; NM_000267.3), that was absent from both parents and classified as likely pathogenic according to the ACMG guidelines. The patient responded well to initial treatment with intravenous methylprednisolone and was subsequently started on interferon-beta (IFN-beta-1a) as a first-line treatment for MS. The initial right optic nerve abnormalities improved in subsequent MRI studies (Fig. 1d, e).

Two years after diagnosis and treatment with IFN-beta, the patient presented with another episode of optic neuritis along with internuclear ophthalmoplegia and one-and-a-half syndrome. The patient also reported a 5-day history of hypoaesthesia below the waist and bilateral lower limb numbness worse under the knee region, along with mild left lower limb ataxia. A subsequent MRI revealed enlargement of the known lesion in the T6/7 spinal cord level that was enhancing, as well as new T2-hyperintense lesions in the genu of the corpus callosum and adjacent to the posterior horn of the right lateral ventricle, with subtle contrast enhancement in some of the new lesions. The rest of the known lesions remained unchanged (Fig. 2). Following this, the patient was considered to have a highly active relapsing-remitting

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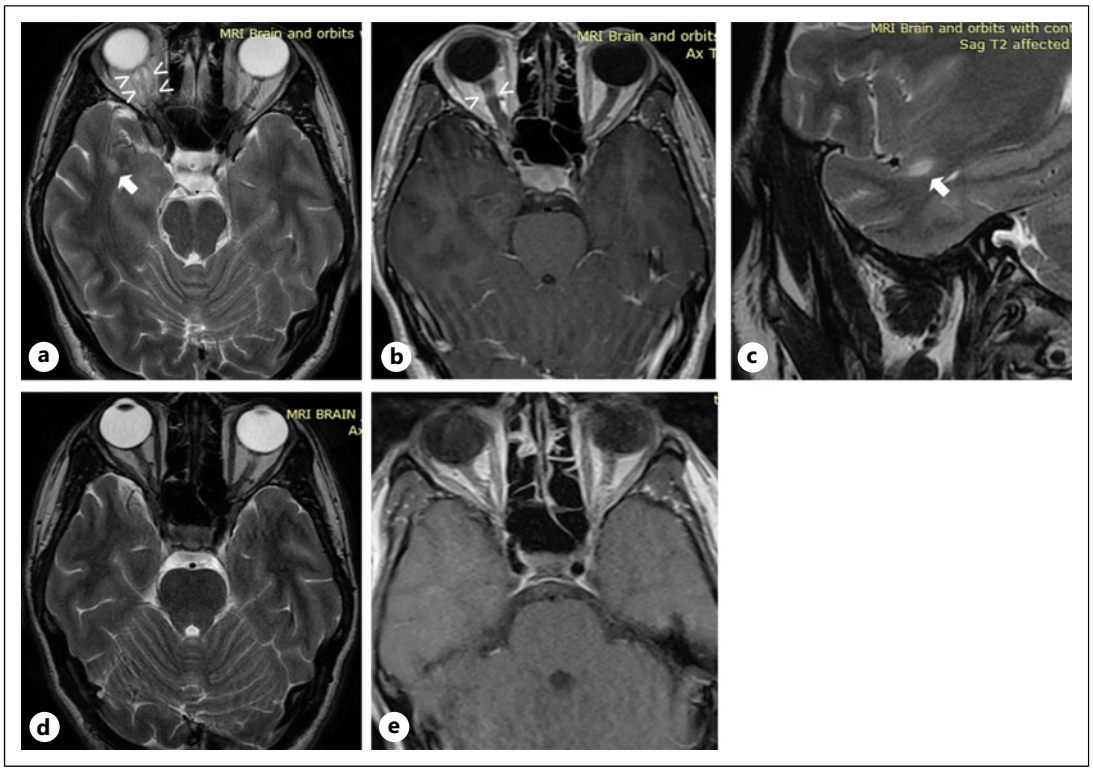

Fig. 1. Representative axial (**a**) T2-weighted image from an initial MRI study of the brain and orbits showing T2-hyperintense lesions in the intracanalicular portion of the right optic nerve (open arrowheads in **a**), with contrast enhancement of the right optic nerve after gadolinium administration (arrowheads in **b**). Both the axial and sagittal (**c**) images showed also a T2-hyperintense lesion in the right anterior temporal lobe (arrows in **a** and **c**). **d**, **e** In the repeat MRI study following treatment, there is resolution of inflammatory changes in the right optic nerve as shown by the reduction of T2 signal abnormality (**d**) and no further contrast enhancement (**e**).

type of MS (RRMS), inadequately controlled with INF-beta. After a negative anti-JCV antibody test, she was initiated on a monthly IV natalizumab treatment. She has responded well and has remained clinically stable over the next 18 months, with complete resolution of the previous neurological deficits besides residual mild colour desaturation in the right eye (last EDSS score 0.5). Subsequent MRI studies of the brain and spinal cord also showed no further new or active lesions since the initiation of natalizumab.

Discussion

In this case study, we report the first patient with MS and NF1 in Cyprus. This patient initially presented with signs and symptoms of MS and was later diagnosed with NF1 due to atypical radiological features and associated peripheral signs. The co-existence of MS with NF1 is rare but has been reported in the literature, with a study suggesting an increased risk of developing MS with NF1 [6]. This patient had the relapsing-remitting type, even though Elsayed et al. [5] cited previous studies that demonstrated that the most common form of MS in NF1 patients is the primary progressive type, which is hypothesised to be associated with an oligodendrocyte myelin glycoprotein gene mutation [7].

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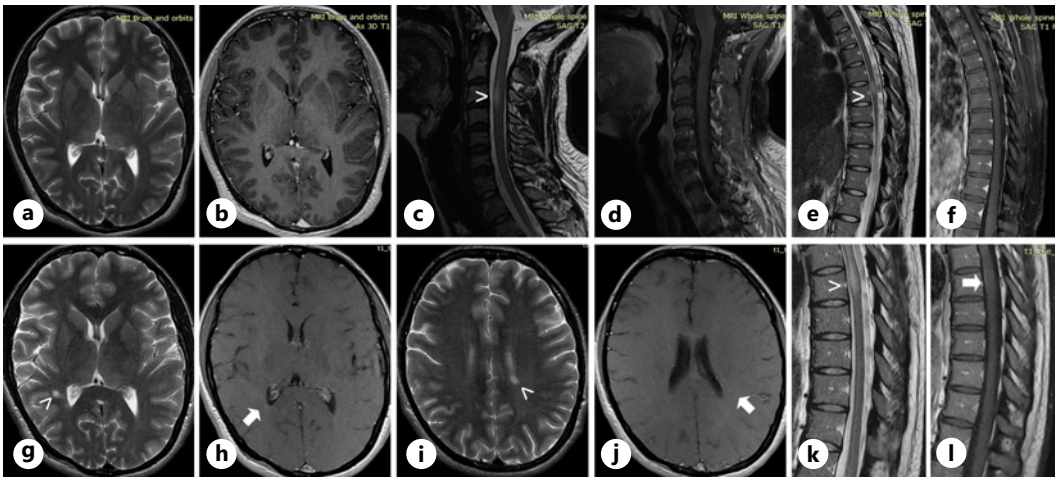

Fig. 2. Representative images from initial (**a–f**) and repeat (**g–l**) MRI studies of the brain and spinal cord. **a–f** Images of initial MRI studies including axial T2-weighted (**a**) and T1 with gadolinium (**b**) from the brain at the level of the internal capsule; sagittal T2 images of the cervical spinal cord (**c**) showing the high signal lesion at C3 level (open arrowhead) which was not enhancing in T1 with contrast (**d**); and thoracic spinal cord T2 (**e**) and T1 with contrast (**f**) images showing a non-enhancing lesion at T6-7 level (open arrowhead). **g–l** In the repeat MRI study 2 years after diagnosis and treatment with IFN-beta-1α, axial images of the brain demonstrate new periventricular lesions (arrowheads) in T2 images (**g** and **i**) with subtle contrast enhancement (arrows) in corresponding T1 images with contrast (**h** and **j**). Furthermore, thoracic spinal cord images (**k**, **l**) show enlargement and subtle contrast enhancement of the T6-7 spinal cord lesion (T2 image in **k** and T1 with contrast in **l**).

However, due to the rarity of such patients, there is a lack of adequate epidemiological data and treatment guidelines, while diagnosis and differentiation of lesions on MRI can be challenging.

As this patient was diagnosed concomitantly with both conditions, differentiating which lesion is due to which condition can be challenging, as both FASI and MS lesions show high signal on T2-weighted MRI [2, 8], while MS lesions are hypointense and FASI are isointense in T1-weighted images. Gadolinium enhancement can be useful, as active MS lesions typically enhance while FASI do not, except in rare cases where they do enhance focally [8]. While neurofibromas also enhance, they have a more heterogeneous T2-hyperintensity [9]. Despite that, these characteristics are not always present, making it difficult to distinguish whether a non-enhancing lesion is an old MS lesion or a FASI, or whether a gadolinium-enhancing lesion is a neurofibroma or an active MS lesion. Location can be helpful in this case, as MS and NF1 lesions have typical locations in which they occur. Considering the MAGNIMS criteria [2], this patient had periventricular and spinal cord lesions that are typical for MS, along with subcortical lesions involving the centrum semiovale, frontal, and temporal lobes which were also suggestive of MS lesions as they stopped exhibiting contrast enhancement in follow-up MRIs and after treatment initiation. In terms of NF1-related lesions, neurofibromas were clearly identified in this patient as subcutaneous lesions in the occipital and temporal regions, which remained unchanged on follow-up MRIs. Furthermore, FASI does not typically occur in the periventricular area or the corpus callosum but can involve the brainstem, the cerebellum, and the hippocampus [7, 8]. The patient had no lesions in the cerebellum but had unchanged and non-enhancing diffuse signal changes in the hippocampus and thalami which are suggestive of FASI. Nevertheless, there are overlaps and exceptions in terms of lesion location, contrast enhancement, and signal intensity, making lesion differentiation particularly challenging.

The immune system has a critical role in the identification and destruction of cancer cells. As a result, MS patients receiving long-term DMTs may be at higher risk of developing cancer [10]. This risk, however, can be further magnified in the presence of a tumour-predisposing condition like NF1. As patients with NF1 have a 10–12% overall risk of developing a malignancy [11], clinicians need to balance out the therapy-associated risk of cancer with the prevention of MS-associated neurological disability in patients diagnosed with both conditions. This is particularly challenging due to the rarity of these cases, but also due to the lack of an established relative risk of malignancy in MS patients taking long-term DMTs. In addition to that, no clear guidelines exist for the treatment of MS patients with any other co-morbid cancer either [10]. This eventually prevents the clinician from objectively evaluating the risks and benefits of treatment.

As this patient had a highly active form of RRMS, a step-up treatment with Natalizumab was deemed appropriate since it is a relatively safe, effective, and well-tolerated choice for highly active RRMS patients [12, 13], especially when started early in DMT-naïve patients [14]. The most well-known side effect of natalizumab is the development of progressive multifocal encephalopathy, which can be effectively prevented with regular JC antibody screenings. Concerning cancer risk, a disproportionality analysis done using the World Health Organisation (WHO) pharmacovigilance database showed higher incidences of cancer among MS patients on natalizumab, fingolimod, and dimethyl fumarate compared to ocrelizumab, alemtuzumab, and glatiramer acetate [15]. In our case, fingolimod was avoided due to a more established risk of skin cancer, and treatment with natalizumab was continued as adequate and long-term control of the patient's MS was achieved.

Currently, there is only one published study that demonstrates a highly active MS and NF1 patient adequately controlled with natalizumab [11], and further work is needed to establish the relative risk of cancer in MS patients receiving DMTs, as well as comparative studies on the effectiveness of different DMTs in highly active RRMS. This can give objective guidance on the prevention of neurological disability in patients who are predisposed to cancer, as in this case.

CARE Checklist

The CARE checklist has been completed by the authors and is available as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536463).

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images and is available on request. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Marios Lemonaris: writing – original draft, investigation, and data curation. Kleopas A. Kleopa: writing – review and editing, supervision, patient consent, and providing all relevant data.

Data Availability Statement

All data generated or analysed during this study are included in the article and its online supplementary material and were taken from the listed references, except the data related to our patient's investigations and results. Further enquiries can be directed to the corresponding author.

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