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Case Report

Advanced neuroimaging in Balo's concentric sclerosis: MRI, MRS, DTI, and ASL perfusion imaging over 1 year

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ABSTRACT

Balo concentric sclerosis (BCS) is a rare, atypical demyelinating disease, which may rapidly progress to become severe and fatal. Advanced neuroimaging has proven helpful for early diagnosis, classification, prognostication, and monitoring of progression in multiple sclerosis, but has not been fully explored in BCS. We present the case of a 27-year-old woman with BCS in whom advanced neuroimaging was used to correlate the evolution of disease with clinical findings over the course of 1 year. Magnetic resonance imaging, magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and arterial spin labeling cerebral perfusion were obtained at presentation (Day 0), and at Day 67 and Day 252. Imaging features include multilayered concentric ring lesion, reduced diffusion along the rim, hypoperfusion with possible mild central hyperperfusion, and MRS findings of increased choline, decreased N-acetylaspartate (NAA), and possible presence of lactate and/or lipid peak. DTI tractography and relative apparent diffusion coefficient analyses correlated with clinical symptoms and may help to determine extent of white matter tract injury and prognosis.

1. Introduction

Balo concentric sclerosis (BCS) is a rare demyelinating disease, historically thought to be severe and fatal. Three courses are recognized: a self-limited monophasic illness, relapsing-remitting demyelination, and classically described primary rapidly progressive disease [1].

Pathologically, it is characterized by a lesion consisting of rings of demyelination alternating with rings of intact myelin. Tissue biopsy of BCS lesions show cerebral white matter oligodendrocyte loss within regions of demyelination including foamy macrophages, activated microglia, reactive astrocytes, and areas of axonal loss similar to that in multiple sclerosis (MS) lesions [2]. Lesions form radially from a central venule where there is loss of blood brain barrier integrity with macrophage and microglia activation. The formation of concentric rings may be an individual response determined by genetic factors, as supported by the finding that layers of

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preserved myelin in between lesions contain specific neuroprotective peptides [3].

MRI features include large concentric ring-like lesions in white matter with alternating hyper- and hypointense bands on T2-weighted images. Active lesions have enhancing and non-enhancing layers on contrast-enhanced T1-weighted images [4]. Magnetic resonance spectroscopy (MRS) features often demonstrate increased choline, decreased N-acetylaspartate (NAA), and the presence of lactate and/or lipid peaks [4–6]. There are few reports of cerebral perfusion studies demonstrating lesional hypoperfusion with possible mild central hyperperfusion, presumably corresponding to a deep venule [7]. To our knowledge, there is only one report of diffusion tensor imaging (DTI) in an adult with BCS showing disruption of the corticospinal tract, which correlated with location and size as confirmed by biopsy [8].

Advanced neuroimaging has proven helpful for early diagnosis, classification, prognostication, and monitoring of progression in MS, but has not been fully explored in BCS. DTI can be used to evaluate the integrity of myelinated tracts located in the white matter. Increased apparent diffusion coefficient (ADC) and decreased fractional anisotrophy (FA) are markers of white matter lesions and correlate with disease progression and cognitive decline in MS [9]. MRS evaluates changes in metabolite concentrations, generally showing increased lactate and choline, and decreased NAA in acute MS lesions, which correlate with reduced executive function and attention [10]. Magnetic resonance perfusion studies, such as arterial spin labeling (ASL), can detect and diffuse local hypoperfusion in MS, which correlate with clinical disability and neuropsychological decline [10].

We characterized advanced neuroimaging and correlated evolution of a BCS lesion with clinical findings over the course of 1 year.

2. Case report

A previously healthy Caucasian 27-year-old woman, with no significant family history of autoimmune disease, presented with sudden onset of left facial weakness, without fever, coryza, earache, or head trauma. The examination was notable only for left facial weakness involving the upper and lower face, without any other cranial nerve or long tract involvement.

She was diagnosed with Bell's palsy and treated with 3 days of valacyclovir and 12 days of oral prednisone at 60 mg daily. After 1 day, her left facial weakness persisted, with the addition of left thumb numbness. She continued on another 5 days of oral prednisone without improvement, and developed left hand incoordination with typing.

MRI of the brain showed a multilayered concentric ring lesion in the right centrum semiovale (Fig. 1A and B). After initial review with the patient still in the MRI scanner, the neuroradiologist prescribed ASL perfusion, MRS, and DTI for further characterization of the lesion.

Cerebral blood flow (CBF) map from ASL showed regional hypoperfusion with central minimally increased perfusion within the lesion (Fig. 1C). Isotropic combined diffusion-weighted image (isoDWI) and mean diffusivity map from DTI showed a ring of relatively reduced diffusion along the rim of the lesion (Fig. 1D and E). Directionally-encoded color FA map showed near-complete loss of normal white matter anisotropy in the region of right corticospinal tract (Fig. 1F), which was confirmed with DTI tractography demonstrating disruption of inferolateral subcortical branches of the right corticobulbar and corticospinal tracts (Fig. 2). MRS showed increased choline, decreased NAA, and small lactate doublet peak that is inverted at TE 144 ms (Fig. 3).

With imaging diagnosis of BCS, she was started on 3 days of intravenous methylprednisolone at 1 g daily. She had complete resolution of her symptoms upon completion of her steroid treatment.

CSF studies from lumbar puncture performed after intravenous steroid administration showed no evidence of blood brain barrier disruption or intrinsic inflammation, with normal protein, glucose, Q-albumin ratio, IgG Index, IgG-Albumin ratio, and IgG synthesis rate. There were no red blood cells per mm^3, two white blood cells per mm^3, glucose 67 mg/dl, and protein 7.0 g/dl. No oligoclonal bands were detected, and myelin basic protein was normal at 0.88 ng/dl.

Serological tests for ACE, SSA, SSB, ANA, and rheumatoid factor levels were not elevated. AQP4 IgG or MOG IgG were not tested as she did not have any evidence of optic neuritis.

Repeat brain MRIs after steroid treatment at 67 and 252 days after presentation showed significantly decreased lesional enhancement, resolving diffusion changes, and no new lesions (Fig. 4).

One year after initial presentation, she remained symptom-free without any residual neurologic deficit.

3. Methods

3.1. *Magnetic resonance imaging (MRI)*

MRI of the brain was acquired on a 3.0 T clinical MRI scanner (Signa Excite HDxt, GE Medical Systems, Milwaukee, WI) using an 8-channel head coil. ADC was calculated using MRI with diffusion weighted imaging (DWI).

3.2. *Arterial spin labeling (ASL)*

ASL was obtained using 3D pCASL (TE 10 ms, TR 4600 ms, TI(PLD) 1525 ms, NEX 3, slice thickness 4 mm, matrix 128 × 128, FOV 24 cm). CBF map was reconstructed from ASL.

3.3. *Magnetic resonance spectroscopy (MRS)*

Single-voxel MRS was obtained using both short TE (35 ms) and long TE (144 ms) PROBE-PRESS (TR 1500 ms, FOV 24 cm) with 2 × 2 × 2 cm^3 voxels and surrounding saturation bands placed overlying the right centrum semiovale lesion as well as in the normal-appearing left centum semiovale for control.

3.4. *Diffusion tensor imaging (DTI)*

DTI with 25 diffusion gradient directions was obtained using spin-echo EPI (TE 86 ms, TR 1,4000 ms, b-value 1000 s/mm^2,

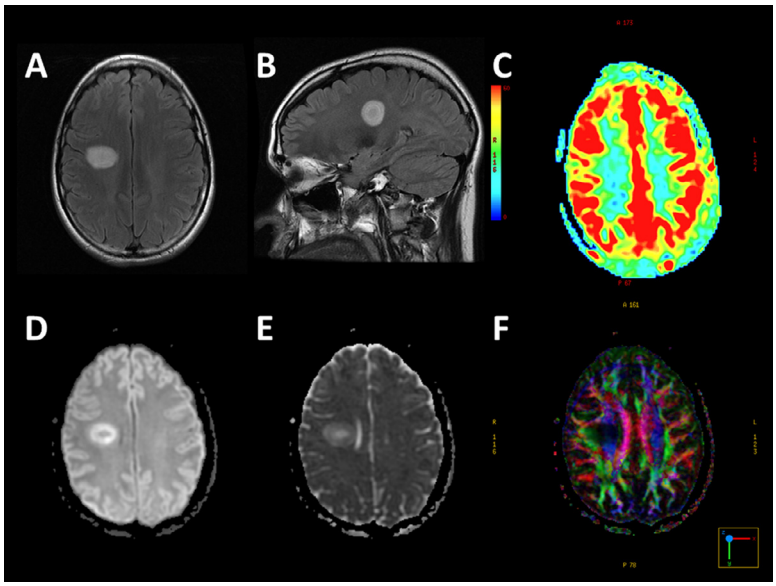

Fig. 1 – Magnetic resonance imaging of Balo concentric sclerosis. (A) Axial and (B) sagittal T2-weighted FLAIR images show typical multilayered concentric ring lesion in the right centrum semiovale. (C) Cerebral blood flow map shows regional hypoperfusion with central minimally increased perfusion within the lesion. (D) Isotropic combined diffusion-weighted image and mean diffusivity map show a ring of relatively reduced diffusion along the rim of the lesion. (F) Directionally-encoded color fractional anisotrophy map shows near-complete loss of normal white matter anisotropy in the region of right corticospinal tract.

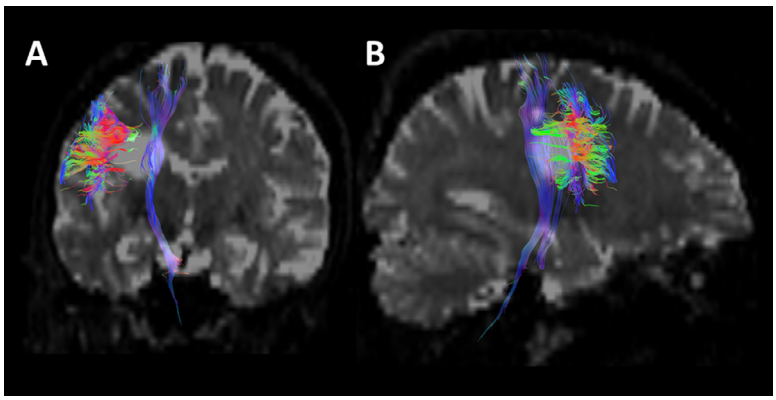

Fig. 2 – Diffusion tensor imaging (DTI) imaging of Balo concentric sclerosis. (A) Coronal and (B) sagittal projectional images of right corticospinal and corticobulbar tracts from DTI tractography show disruption of inferolateral subcortical branches of the right corticobulbar and corticospinal tracts.

slice thickness 2.9 mm, matrix 128 × 128, FOV 24 cm). Isotropic combined diffusion-weighted image (isoDWI) and (E) mean diffusivity map was calculated from DTI.

3.5. *Tractography*

Tractography was reconstructed from DTI using Diffusion Toolkit and TrackVis (MGH/HST Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA) with second-order Runge–Kutta propagation algorithm, 35° angle threshold, and minimum FA threshold automated by software.

4. Discussion

Imaging differential diagnoses for BCS include other demyelinating disease, subacute subcortical infarction, neoplastic lesion such as high-grade glioma and lymphoma, and cerebral abscess.

In this patient, MRI showing multilayered concentric ring lesion involving the right centrum semiovale is pathognomonic for BCS. Regions of concentric ring enhancement and reduced diffusion in BCS are likely related to active demyelination with disturbances in energy metabolism, cytotoxic cell swelling, and hypercellularity from acute

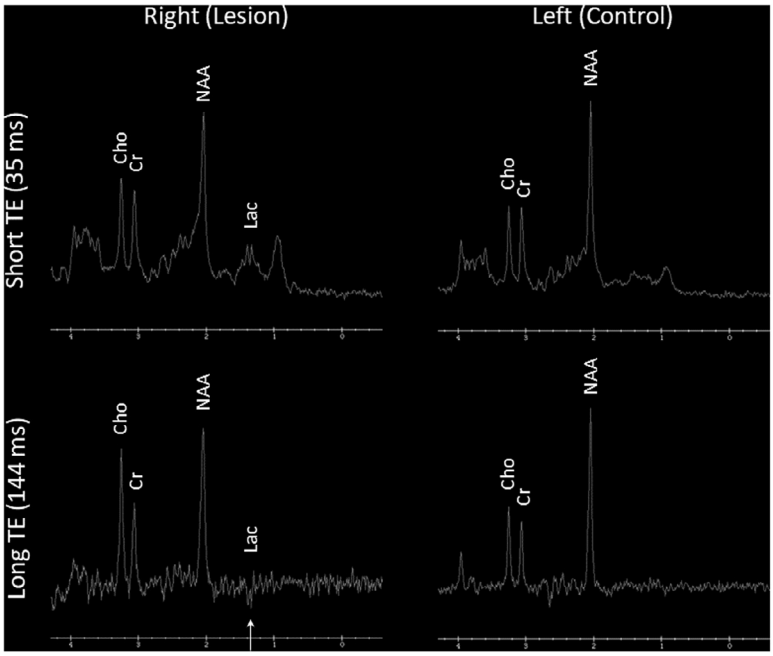

Fig. 3 – Magnetic resonance spectroscopy of Balo concentric sclerosis. MRS using TE 35 ms (top row) and echo time (TE) 144 ms (bottom row). In both cases, choline (Cho) is slightly increased; N-acetylaspartate is slightly decreased, and small lactate doublet peak is present within the lesion.

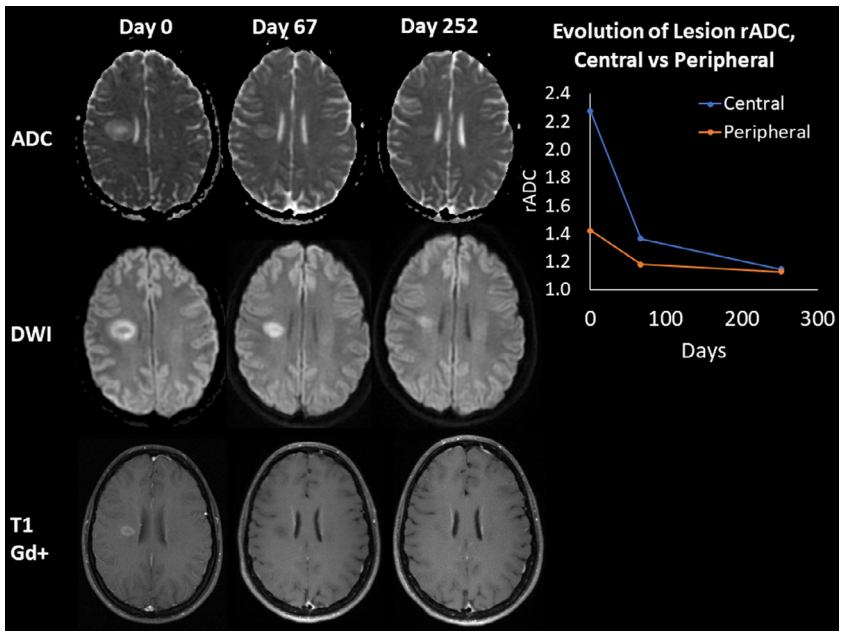

Fig. 4 – Evolution of Balo concentric sclerosis over time. Axial diffusion weighted imaging, apparent diffusion coefficient (ADC) map, and postcontrast T1-weighted images of the lesion acquired at presentation (Day 0), Day 67, and Day 252 show evolution of diffusion changes and contrast enhancement with time. Graph of relative ADC over time shows relatively reduced diffusion in the periphery compared to the central part of the lesion. This was most pronounced at presentation, decreased but still present at Day 67, and nearly resolved at Day 252.

inflammation possibly contributing to reduced diffusion, with myelin preservation related to expression of neuroprotective peptides [1–3]. The patient's clinical findings negatively correlated with enhancement and diffusion restriction on MRI, suggesting that these imaging techniques can measure treatment response and prognosis.

Acute demyelination, like acute infarctions, can be associated with reduced diffusion, as measured by ADC or FA, with similar evolution of these parameters as the lesions progress from acute to chronic stages. While acute infarctions do not enhance, distinguishing them from the plaques of acute demyelination, subacute infarctions can enhance. The enhancement, however, is typically more uniform and not concentric ring-like, as in BCS. We show that the time-course of diffusion changes associated with BCS is prolonged relative to that typical of ischemic lesions, with reduced diffusion lasting for several weeks. Cerebral abscesses show ring enhancement but often have reduced diffusion centrally, and are associated with significant surrounding vasogenic edema.

Although high-grade glioma and lymphoma also display ring enhancement and reduced diffusion from hypercellular tumor, these neoplastic lesions are often infiltrative with mass effect and demonstrate hyperperfusion and significantly increased choline with choline/creatine ratio >2 on MRS. These choline/creatine ratios are not significantly different from demyelinating lesions, but increased neuronal destruction in high-grade gliomas leads to relatively reduced NAA/creatine ratios as compared to demyelinating lesions [11]. As in our patient, MRS features of BCS typically include increased choline from cellular membrane turnover, decreased NAA from neuronal injury (but not as much as high-grade gliomas), and presence of lactate and/or lipid peaks from anaerobic metabolism and membrane lipid release from severe tissue injury, respectively [4–6]. The decreased NAA in demyelination may be reversible, possible reflecting decreased mitochondrial synthesis from transient neuronal dysfunction [12,13].

CBF, as measured by ASL, is usually decreased in demyelinating lesions, while it is usually increased in high-grade gliomas [14]. Similar to our findings, regional hypoperfusion with possible mild central hyperperfusion, presumably related to a deep venule, has been described in BCS [7]. The mechanisms may be complex as other reports have suggested that CBF may be increased in acute demyelination due to disruption of the blood brain barrier, and decreased in chronic demyelination due to axonal loss and regional hypometabolism [15].

DTI tractography can determine the integrity of white matter tracts, which in this case demonstrated disruption of predominantly the right corticobulbar tract, and, to lesser degree right corticospinal tract. These corresponded well to the patient's primary complaint of left facial weakness and subsequent development of subjective left hand incoordination.

Due to the rarity of BCS, no clinical trials have determined the optimal treatment for the condition. Most reported cases have used oral and intravenous steroids. There are case reports of varying responses to mitoxantrone, intravenous immunoglobulin, azathioprine, and plasmapheresis [16–19]. Our patient received intravenous steroids with complete remission of her symptoms and has not required immunomodulatory therapy in the year following initial presentation.

5. Conclusion

This report demonstrates and correlates clinical and advanced neuroimaging techniques including MRI, MRS, DTI and ASL cerebral perfusion in evaluating a patient with BCS. BCS is a rare demyelinating disease, characterized pathologically by a lesion consisting of rings of demyelination alternating with rings of intact myelin. Biopsy may be avoided if neuroimaging supports the diagnosis. Imaging features include multilayered concentric ring lesion, reduced diffusion along the rim, hypoperfusion with possible mild central hyperperfusion, and MRS findings of increased choline, decreased NAA, and possible presence of lactate and/or lipid peak. DTI tractography and relative ADC analyses may be helpful in determining extent of white matter tract injury and prognosis. Improved clinical awareness and advanced neuroimaging techniques can lead to early and accurate diagnosis and treatment.

Conflict of interest

No financial disclosures or conflicts or interests.

Ethical approval

This case is reported in line with the ethics required by the journal.

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