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Balo's concentric lesions with concurrent features of Schilder's disease in relapsing multiple sclerosis: neuropathological findings

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ABSTRACT

Atypical inflammatory demyelinating syndromes are rare neurological diseases that differ from multiple sclerosis (MS), owing to unusual clinicoradiological and pathological findings, and poor responses to treatment. The distinction between them and the criteria for their diagnoses are poorly defined due to the lack of advanced research studies. Balo's concentric sclerosis (BCS) and Schilder's disease (SD) are two of these syndromes and can present as monophasic or in association with chronic MS. Both variants are difficult to distinguish when they present in acute stages. We describe an autopsy case of middle-aged female with a chronic history of MS newly relapsed with atypical demyelinating lesions, which showed concurrent features of BCS and SD. We also describe the neuropathological findings, and discuss the overlapping features between these two variants.

Keywords

Multiple Sclerosis; Atypical Inflammatory Demyelination; Balo's Concentric Sclerosis; Schilder's Disease; Pathology

CASE REPORT

A 45-year-old woman presented in another hospital with a history of generalized tonic clonic seizure and acute confusion. She was admitted to the intensive care unit for close observation. Her past medical history revealed that she had been diagnosed clinically with multiple sclerosis (MS) in 2005, and had shown a good response to various combinations of methylprednisolone, cyclophosphamide, and interferon. During the course of her illness, she had a history of multiple admissions to the hospital with several relapses between 2005 and 2006. Her disease settled in the remitting phase for 7 years. In this current admission, her medical condition deteriorated and she became unresponsive to the usual medical

treatment. Brain magnetic resonance imaging (MRI) with gadolinium contrast showed space-occupying lesions in the right and left frontal white matter, with the left showing concentric rings with an onionskin pattern (Figure 1).

Blood chemistry revealed a normal blood count and normal renal and liver function. HIV anti-nuclear antibody, anti-dsDNA, rheumatoid factor, and anti-phospholipid antibody were negative. Cerebrospinal fluid (CSF) analysis was negative for anti-aquaporin-4 (anti-AQP4) antibody with absent oligoclonal band immunoglobulin G (IgG). The concentration of very long-chain fatty acids was normal. The patient was treated with high-dose

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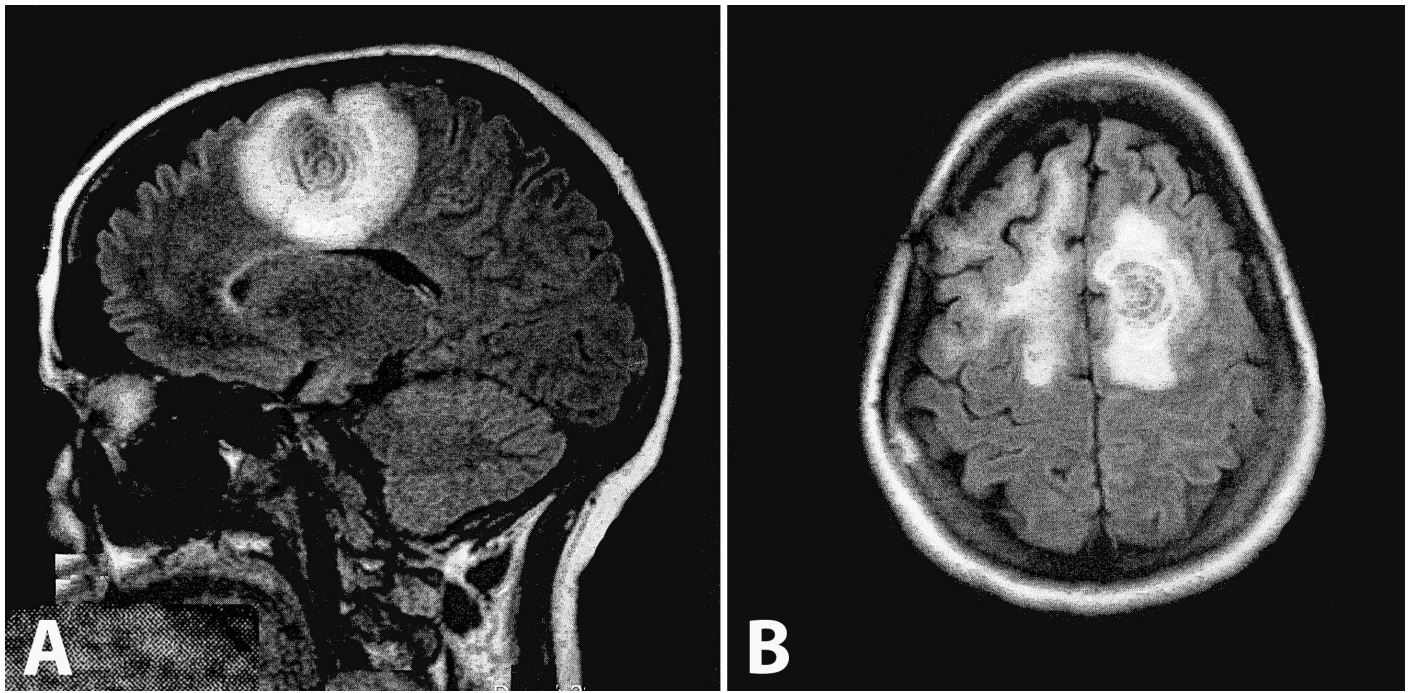


Figure 1. Brain MRI (T1 weighted images with contrast) shows a space-occupying lesion in the left frontal white matter, surrounded by mild edema. The lesion has a concentric onion-skin-like pattern (**A** - sagittal plane and **B** axial plane).

methylprednisolone, after which her clinical symptoms did not improve. Unfortunately, she had a sudden cardiorespiratory arrest from which she could not be resuscitated. The family requested a general autopsy including the brain and spinal cord. The general autopsy revealed a pulmonary embolus as a cause of her death. The formalin-fixed brain and spinal cord were referred to our institution for neuropathological consultation.

NEUROPATHOLOGICAL ASSESSMENT

The fixed brain weight was 1226 g. The whole brain showed a very mild atrophy. The brain-cut protocol was performed. There were symmetrical areas of brown-gray discolorations of the centrum semiovale extending into the digitate white matter. These lesions were found in the anterior part of the right frontal lobe (Figure 2A), the dorsal part of the left frontal lobe (Figure 2B and 2C), and the parietal occipital regions. The left frontal lesion (measuring 2.3×3.3 cm) showed distinct arranged grossly viable laminae with a concentric globe.

The right frontal lesion showed clearly visible subcortical U-fiber (SCUF). The focal lesions in the parietal-occipital regions were partially cystic.

Sections from the left and right frontal lesions were examined using light and electron microscopy. We used different staining protocols on the sections taken from the right and left frontal lobes. Hematoxylin and eosin (H&E) with Luxol fast blue (LFB) (Figure 3A and 4) was the main staining method. We also created combined stains (Bielschowsky silver stain with LFB (Figure 3B) and neurofilament with LFB (Figure 3C), performed on the left frontal lesion to highlight the SCUF, to examine the axonal process, and to assess the myelin in relation to the axons.

With the aid of the pathological staging of CNS demyelination, we found that the left frontal lesion histologically showed an ill-defined area of late active plaque associated with alternating bands of preserved and non-preserved myelin in wavy patterns. Both bands showed preserved axons by neurofilament stain (Figure 3C). The right frontal lesion showed an ill-defined area of late active plaque with a deep loss of myelin (Figure 4). LFB stain showed spared SCUF in both lesions. Both frontal lesions showed typical features of demyelination with few macrophage-engulfed

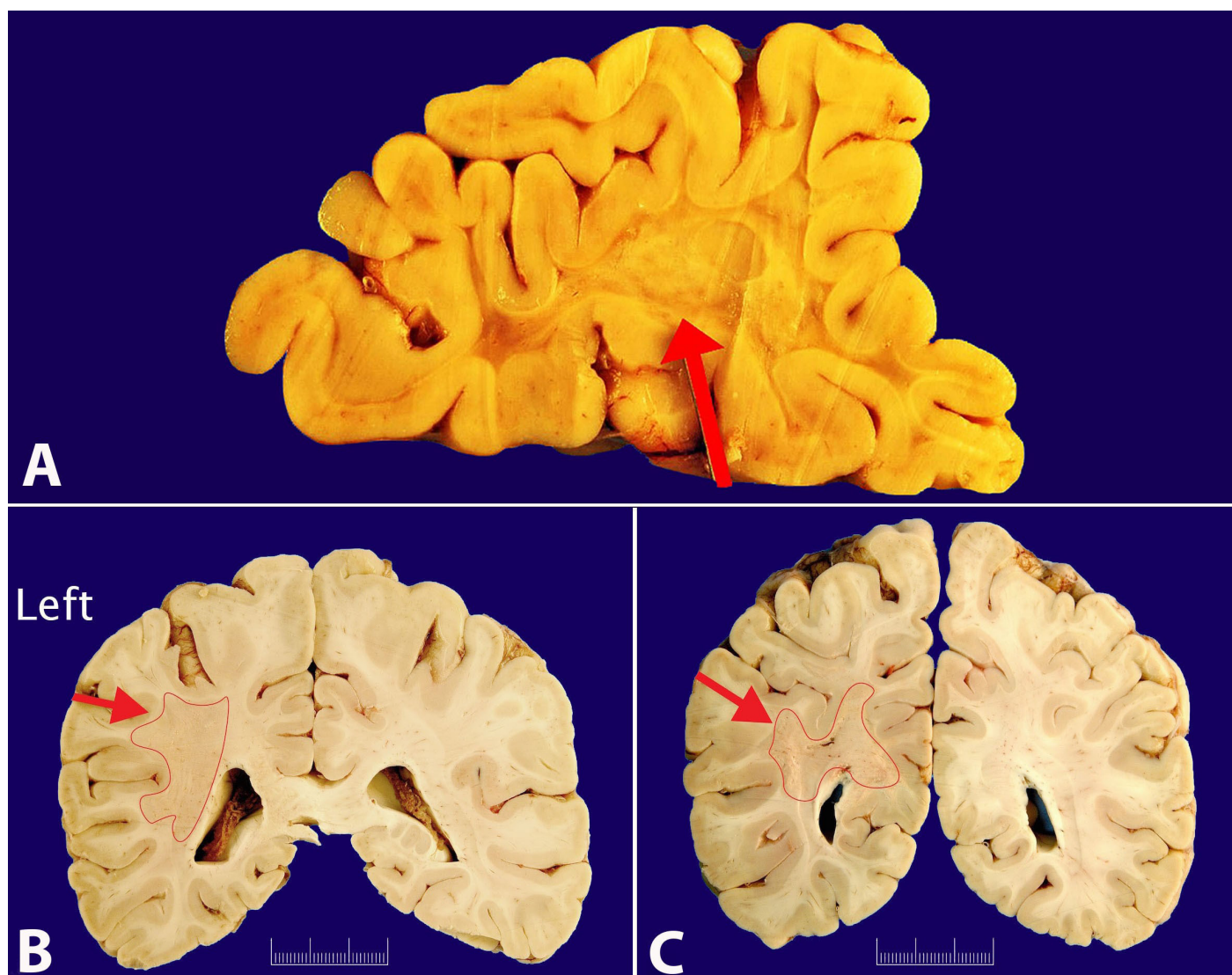


Figure 2. **A** - Gross section of the right frontal lobe showing a brown-gray lesion; **B** and **C** - Gross examination of brain slices showing symmetrical brown-gray discolorations of the centrum semiovale extending into the digitate white matter (red arrow).



Figure 3. Histological sections of the left frontal lesion treated with different stains. **A** - H&E and LFB (10X); **B** - Bielschowsky with LFB (10X); **C** - Neurofilament with LFB (10X). The lesion shows a concentric pattern of myelinated and non-myelinated layers with spared subcortical U-fibers. The neurofilament shows intact axons.

myelin in the main plaque center, scant perivascular lymphocytic cuffs, few macrophages, and gliosis.

There were no features of acute ischemia in the affected areas. Periodic acid-Schiff (PAS) stain showed

no evidence of specific variants of leukodystrophies. The optic nerve, optic chiasm, brainstem, spinal cord, and cerebellum were unremarkable. Ultrastructural examination of poorly preserved fixed tissue only

showed scattered myeloid and zebra bodies (Figure 5). The myelin was degenerated and the axons were somewhat preserved.

DISCUSSION

Atypical inflammatory demyelinating syndromes are rare neurological diseases that differ from MS, owing to unusual clinico-radiological or pathological findings, and poor responses to treatments.¹ These syndromes include neuromyelitis optica, acute disseminated



Figure 4. Histological section of the right frontal lesion treated with H&E and LFB (10X) shows the gradual loss of myelin in deep white matter, which is associated with spared subcortical U-fibers (arrow).

encephalomyelitis, tumefactive demyelination, Balo's concentric sclerosis (BCS), Schilder's disease (SD), and Marburg's MS. If patients present with atypical MRI findings, atypical presentation, or do not respond well to the treatment that is usually effective for MS, these syndromes should be considered. Because some of these syndromes are associated with MS, the overlapping features are poorly defined, and may complicate the diagnosis.

Our patient had a 7-year history of chronic MS. She recently relapsed with newly acute symmetrical demyelinating lesions of the frontal lobe. The left frontal lesion showed Balo's pattern while the right frontal lesion showed demyelination with spared SCUF.

BCS was described in 1928 by a Hungarian neuropathologist: Josef Bal.² It characteristically occurs as a discrete concentrically layered lesion in the cerebral white matter.² This distinctive appearance helps to distinguish it from other demyelinating lesions of conventional MS. The average age of onset of BCS is 34 years and seems to be more common in patients of East Asian origin.³ BCS may occur simultaneously with MS-like lesions or may herald the onset of MS, indicating that, in certain patients, they seem to be different manifestations of the same disease rather than separate pathological entities.⁴ It can occur with anti-AQP4 antibody seropositive and seronegative neuromyelitis optica.⁵ On brain MRI, the lesion appears as concentric rings with alternating high and low

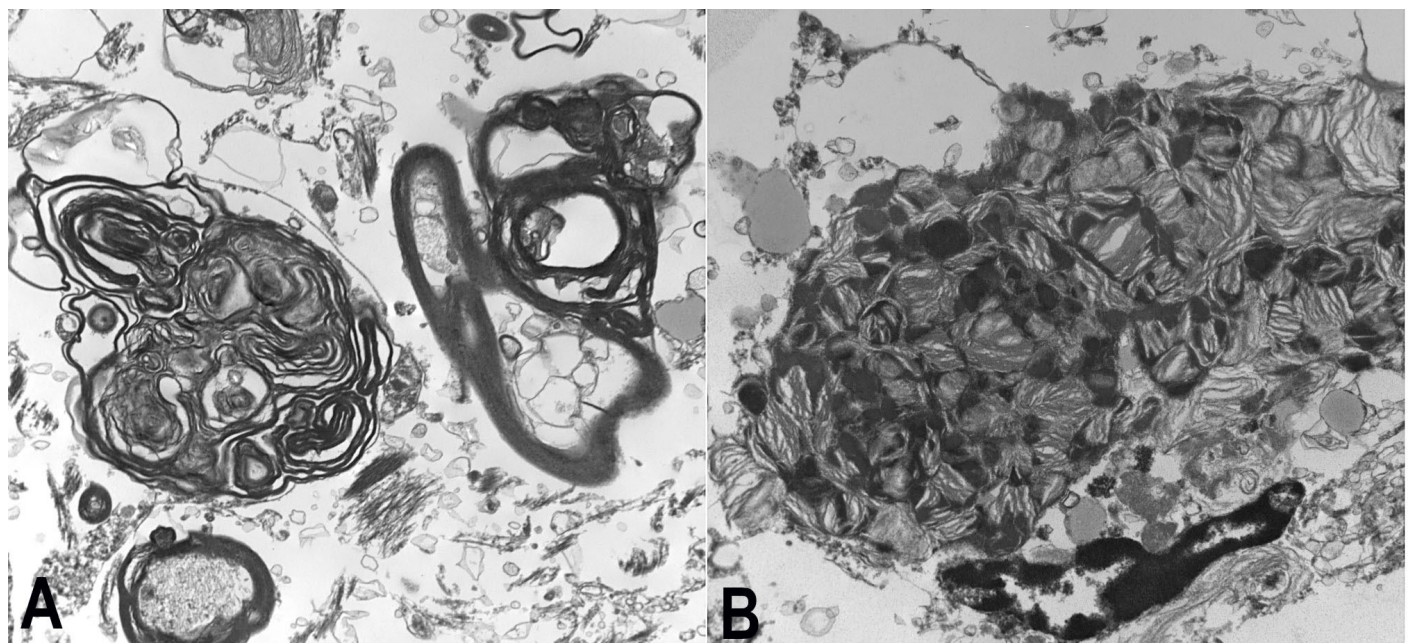


Figure 5. Ultrastructural examination of the lesion by electron microscopy. **A** - Myeloid bodies; **B** - Zebra bodies.

intensity with minimal surrounding edema. It can be multiple at onset or occur as solitary lesions.⁶ Not all patients with BCS have oligoclonal bands: in a study of 11 patients with BCS, CSF synthesis of oligoclonal bands was present in one patient only.⁷

Pathologically, Balo's lesions are well described and classically consist of cerebral white matter oligodendrocytes loss and demyelination, with sparing of the cortical grey matter.⁸ The lesions have an alternating ring appearance of relative myelin preservation and loss with relative axonal sparing, which gives them a so-called onion bulb appearance.⁹ Astrocytopathy has been proposed as a hallmark feature of BCS.⁸

Several hypotheses have been proposed to explain the pathogenesis of the concentric lesions. The lesions seem to arise around a perivenular zone in response to an unknown stimulus that causes macrophages and activated microglia to produce cytokines and oxygen free radicals, which are responsible for inducing demyelination.¹⁰ Hypoxia inducible factor 1 α might give a degree of neuroprotection to preserve the myelin between the rings of demyelination. Astrocyte AQP4 and connexin are markedly reduced in these areas.¹¹

In our patient's case, the left frontal lesion showed features of BCS with preserved SCUF. The right frontal lesion showed a leukodystrophy-like pattern that involved the centrum semiovale to the digitate of white matter. These features can be seen in Schilder's variant.

SD, also known as myelinoclastic diffuse sclerosis, was first described by Schilder in 1912.¹² It is a sporadic atypical demyelinating brain disease that usually affects children. However, It can also occur in the third and fourth decades of life and appears to respond to vigorous treatment with corticosteroids. This rare disease results in formation of one or two bilateral large tumefactive plaques.¹³ In 1986, Poser et al.¹³ established diagnostic criteria for the non-invasive diagnosis of SD. These criteria can be summarized as follows: (i) clinical symptoms and signs atypical for an early course of MS; (ii) a normal CSF, or atypical for MS; (iii) one or two symmetrical bilateral plaques measuring at least 3 × 2 cm and involving the centrum semiovale of the cerebral hemispheres; (iv) no fever, viral or mycoplasmal infection, or vaccination preceding the symptomatology; and (v) a normal serum concentration of very long-chain fatty acids. Additionally, it was noted that in SDs, CSF-restricted oligoclonal bands are generally absent, and that large bilateral areas of demyelination were mandatory for the diagnosis.¹⁴ Some cases of SD represent adrenoleukodystrophy or "transitional" cases with MS. Adrenoleukodystrophy has been ruled out through clinical presentation, biochemical tests, and PAS.

The distinction between BCS and SD is summarized in Table 1.

Table 1. The distinction between Balo concentric sclerosis (BCS) and Schilder's disease (SD)

	BCS	SD
Age and ethnicity	Middle aged, East Asian	Children or early young – any ethnicity
Location	Cerebral white matter	Cerebral white matter (semiovale)
Presentation	Monophasic or with MS	Monophasic or with MS
CSF-anti-AQP4 antibody	Can be positive	Negative
CSF-oligoclonal band IgG	Negative	Negative
VLCFA	Normal	Normal
Multiplicity	Always solitary	Always multiple
Symmetry	Usually asymmetrical	Usually symmetrical
Pathology	Concentricity	Concentricity can be present
Subcortical U-fibers	Never spared	Spared
Astroglia	Dense	Mild
Response to treatment	None	None
Outcome	Poor	Poor

AQP4 = aquaporin 4; CSF = cerebral spinal fluid; IgG = immunoglobulin G; MS = multiple sclerosis; VLCFA = very long-chain fatty acid.

CONCLUSIONS

Atypical inflammatory demyelinating syndromes are rare neurological diseases with unusual clinicoradiological and pathological findings. BCS and SD are rare variants of this spectrum, which can occur simultaneously with MS. They are difficult to distinguish when they present at acute stages. The possible theory for our patient's case was that the decedent's MS was inactive for years then suddenly relapsed with atypical Balo's lesions that asymmetrically progressed to Schilder's pattern.

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