

Balò's concentric sclerosis in a case of cocaine-levamisole abuse

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Daniela Grasso¹ , Carmela Borreggine¹, Giulia Castorani²,
Doriana Vergara¹, Lucia Maria Cecilia Dimitri³,
Domenico Catapano⁴, Annalisa Simeone¹
and Teresa Popolizio¹

Abstract

Balò's concentric sclerosis is a rare variant of multiple sclerosis. It belongs to the group of primary inflammatory central nervous system demyelinating diseases having no clear etiology. Peculiar radiological findings on magnetic resonance imaging are alternating rings of demyelinated and myelinated axons resembling an "onion bulb." We report on a case of a patient with cocaine abuse who presented with Balò's-like acute multifocal leukoencephalopathy supported by histological and radiological findings. The abuse of cocaine and its most frequent adulterant, levamisole, may induce ischemic or hemorrhagic stroke and metabolic or multifocal inflammatory leukoencephalopathy. Only a few studies described levamisole-induced leukoencephalopathy mimicking Balò round lesions. Nevertheless, it has not yet been established the correlation between them; it might also be possible that the cocaine/levamisole addiction represents just a coincidence in some of those patients affected by Balò sclerosis disease.

Keywords

Balò's concentric sclerosis, levamisole, cocaine, magnetic resonance imaging, leukoencephalopathy

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Introduction

Balò's concentric sclerosis (BCS) was formerly assessed as one of the atypical forms of multiple sclerosis (including Marburg's disease, tumefactive demyelination, Schilder's disease and acute hemorrhagic leukoencephalitis). It could lead to substantial disability or death within weeks to months of onset; this, historically, was thought to be uniformly fatal also due to its late diagnosis by autopsy postmortem. It mainly occurs in young female adults (range 3–62 years) with a recognized predilection for individuals of South-East Asian ethnicity, especially from southern China, Taiwan and Philippines.^{1,2}

Historically, it had been named leukoencephalitis periaxialis concentrica, based on its earlier definition of "a disease in the course of which the white matter of the brain is destroyed in concentric layers in a manner that leaves the axis cylinders intact."² According to this theory, the pathological process begins in the cerebral white matter around a perivenular zone, the central core and then it spreads outward concentrically, laying down rings of demyelination alternated with rings of preserved myelin, showing relative

axonal sparing. This mechanism leads to a final "onion bulb" appearance.³

BCS can clinically arise as a single manifestation or as any association of neurological symptoms such as weakness, headache, numbness, seizures, aphasia, cognitive difficulty and behavioral changes. This wide range of symptoms is caused by the different site of the BCS lesions: cerebral hemispheres, optic chiasm, brain stem, cerebellum and spinal cord.^{4,5} BCS manifestations could occur as a single and

¹Department of Diagnostic Imaging, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

²Diagnostic Imaging, Postgraduate Medical School, University of Foggia, Foggia, Italy

³Department of Histopathology, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

⁴Complex Operative Unit of Neurosurgery, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Corresponding Author:

Daniela Grasso, Department of Diagnostic Imaging, IRCCS Ospedale Casa Sollievo della Sofferenza, Viale Cappuccini, 1, 71013 San Giovanni Rotondo, Italy.

Email: daniela.grasso@hotmail.it



self-limited event or as repeated flares with relapsing-remitting or primary progressive features. The first investigations described a more frequent primary progressive clinical course of BCS with a poor prognosis. On the other hand, more recent authors report cases with prolonged survival and less severe clinical manifestation of the pathology.⁶

Nowadays, BCS can be detected earlier *intra vitam* by magnetic resonance and, in many cases, it has a favorable prognosis.

Pathognomonic magnetic resonance imaging (MRI) features of BCS include round onion-like lesions made by alternating bands of demyelinated and myelinated white matter. These can be appreciated on T2-weighted images and, additionally, after gadolinium administration, on T1-weighted images as concentric ring enhancement, with gray matter sparing.

Our goal is to describe a case of a patient with chronic intake of cocaine/levamisole who presented BCS, supported by histological examinations.

Case report

A 41-years-old-man addicted to chronic cocaine and alcohol abuse was admitted to our emergency department in a stuporous state and with urinary incontinence. In the previous 15 days he had developed dysarthria, mutism with a prominent drowsiness and psychomotor disturbances. A brain MRI, abdomen and chest computed tomography (CT) were performed in another hospital. MRI brain scan showed multiple roundish lesions in the periventricular cerebral white matter.

On admission, laboratory tests were within normal limits, and the virological screening together with the Quantiferon, HIV and Treponemal tests was negative. Only C-reactive protein value resulted higher than normal (1.18 mg/L).

A cerebrospinal fluid (CSF) examination revealed a high albumin level, no oligoclonal bands and a normal immunoglobulin G index. The electroencephalogram (EEG) recorded low α and θ waves.

Urine toxicologic screening test detected low level of cocaine and it was negative for benzodiazepines, barbiturates, oxycodone, amphetamine, methadone and cannabinoids. The patient's urine samples were not tested for levamisole. No myelin-oligodendrocyte-glycoprotein (MOG) or aquaporin antibodies 4 were documented.

First, the patient underwent a brain CT study which detected multiple hypointense circular lesions in the bihemispheric white matter surrounded by edema.

Brain MRI revealed multiple well-circumscribed concentric lamellar lesions in the bihemispheric white matter involving the corpus callosum; these lesions showed alternate bands of iso-/hypointensity on T1-weighted images and alternate hypo-/hyperintensity on T2-weighted/fluid attenuation inversion recovery (FLAIR) images and presented with a rim of restricted diffusion on diffusion-weighted imaging (DWI; $b=1000$), more obvious on the edge of the lesions.

Apparent diffusion coefficient (ADC) map confirms alternate bands of diffusion restriction, displaying low signal intensity.

After gadolinium intravenous administration, all the lesions demonstrated an "onion-like" patchy enhancement on post-contrast T1-weighted images.

Double inversion recovery (DIR) sequences showed more detailed lamellar structure of the lesions than FLAIR images, thanks to high sensitivity in juxta and subcortical lesions detection.

MR spectroscopy revealed elevated choline and lactate peaks and decreased *N*-acetylaspartate peak (Figure 1).

MRI of the spine showed no evidence of demyelinating lesions. Stereotactic biopsy obtained from frontal right paraventricular lesion showed gliosis and many swollen reactive eosinophilic astrocytes with perivascular cuffing. Axonal stain showed long stretches of intact axon. In addition, perivascular and periventricular macrophages were found (Figure 2). These pathologic findings supported a possible inflammatory/immune-mediated etiology.

The patient was treated with high-dose oral methylprednisolone for 15 consecutive days, after which his clinical symptoms partially improved.

Discussion

Multifocal inflammatory leukoencephalopathy (MIL) in cocaine users has been rarely reported and only a few cases showed Balò's-like or ring-like lesions, caused by adulterants such as levamisole. We described a patient with cocaine abuse who presented with Balò's type acute multifocal leukoencephalopathy.⁷⁻¹⁹

MRI played a central role in the diagnosis of BCS, thanks to the identification of the characteristic "onion bulb" appearance of the lesions. MRI typically shows round and enhancing lesions, characterized by abnormal signal, hypo- or isointense on T1-weighted images and hyper-isointense on T2-weighted images, representing demyelinated and myelinated areas, respectively.

After Gd-DTPA administration, T1-weighted images revealed concentric rings enhancement caused by increased blood-brain barrier permeability and inflammation response for demyelination.^{4,20}

In addition, DWI reports the same concentric pattern with alternating layers of high and low signal intensity. Moreover, the diffusion coefficient map can confirm the presence of restricted diffusion, which is represented as low signal intensity.²¹ MR spectroscopy reveals an increased choline peak and a decreased *N*-acetylaspartate peak, due to demyelination. This peculiar presentation on MRI is highly suggestive of BCS, even if its clinical differential diagnosis is complex because it includes acute disseminated encephalomyelitis (ADEM), neoplasms, infections such as abscesses and, above all, multiple sclerosis. Magnetization transfer imaging demonstrated reduction of the magnetization transfer ratio at the core in acute lesions and less reduction at the

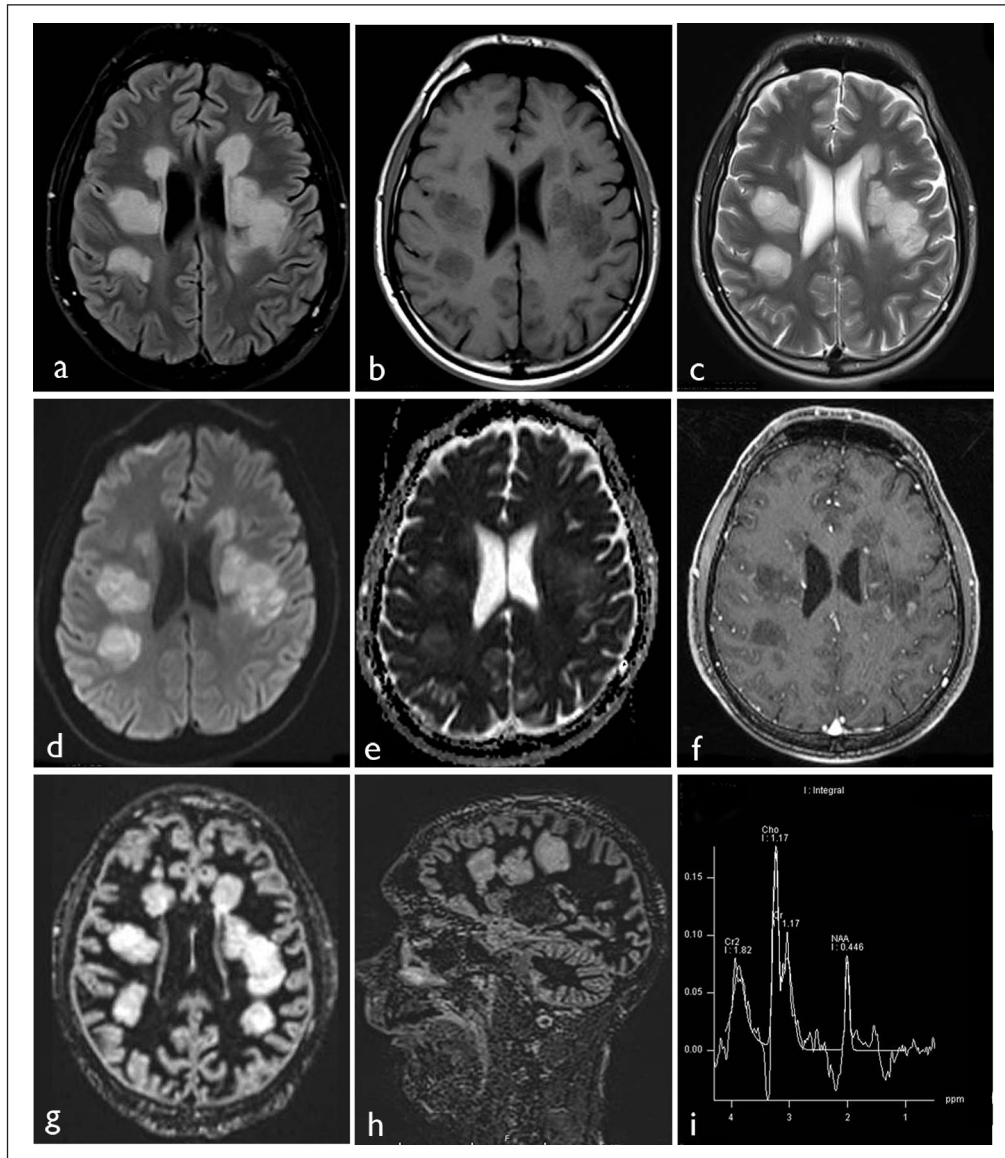


Figure 1. (a)–(i): (a) axial FLAIR, (b) T1 TSE and (c) T2 TSE revealed multiple well-circumscribed concentric lamellar lesions in the bihemispheric white matter involving the corpus callosum that showed alternate bands of iso-/hypointensity on T1-weighted images and alternate hypo-/hyperintensity on T2-weighted/FLAIR images. (d) DWI ($b = 1000$) showed restricted diffusion of the lesions, in particular along the margins. (e) Apparent diffusion coefficient (ADC) map confirms alternate bands of diffusion restriction showing low signal intensity. (f) After intravenous administration of gadolinium, all of the lesions demonstrated an “onion-like” patchy enhancement on post-contrast T1-weighted images. (g, h) % “Double Inversion Recovery sequences (DIR) showed detailed lamellar structure of the lesions due to high sensitivity in detection of juxta and subcortical lesions. (i) MR spectroscopy revealed elevated choline and lactate peaks and decreased *N*-acetylaspartate peak.”

concentric rings.^{1,20,21} Positron emission tomography fluoro-deoxyglucose (PET FDG) showed no increased uptake in Balò’s lesions and can improve the differential diagnosis between other acute demyelinating lesions or brain tumors.²²

Several illicit drugs have been associated with MIL,⁷ and cocaine has been found to be responsible of primary and secondary neurotoxic effects.⁸

Cocaine abuse can cause brain injury with three main mechanisms: vascular alterations, mitochondrial dysfunction and immune-mediated process.^{7,8} Some authors

presumed a direct toxic action of cocaine on myelination processes and an indirect action on the vascular system resulting in ischemic and hemorrhagic stroke through vasospasm, cardioembolism, acute hypertension and vasculitis. Mitochondrial dysfunction is thought to be related to acute/subacute metabolic leukoencephalopathy.^{8–10} More recent evidences reveal a further cocaine-induced mechanism of brain injury. It consists in an immune-mediated mechanism triggered by an adulterant, levamisole, which is currently the most frequent ingredient of cocaine.¹¹

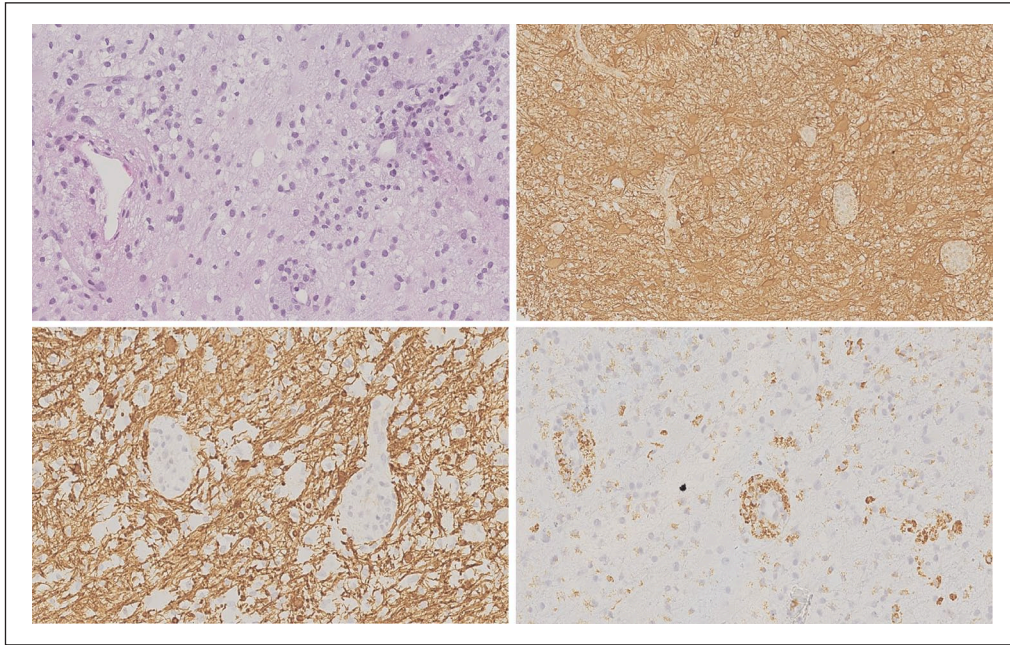


Figure 2. (a)–(d) Stereotactic biopsy obtained from frontal right paraventricular lesion showed ((a) H&E 20×) gliosis and many swollen reactive eosinophilic astrocytes ((b) GFAP immunostain 20×) with a number of instances of perivascular cuffing. Axonal stain showed long stretches of intact axon ((c) neurofilament immunostain 20×) and macrophages were found in a perivascular and parenchymal distribution ((d) CD68 immunostain 20×).

Since 2003, levamisole has been used as cocaine adulterant. Various reasons have been proposed in order to explain this tendency: experiments showed its activity as inhibitor of norepinephrine re-uptake. It is also possible that levamisole conversion in amphetamine-like compounds, such as amorex and related molecules, mimicked the effects of cocaine on the brain. Levamisole may increase both peripheral norepinephrine release (potentiating cocaine's effects) and opioids concentration in the brain.^{12,13}

Literature suggests that the levamisole contamination of cocaine may have contributed to the white matter complications in cocaine abusers.^{9–11,13,14}

Despite the well-established collateral effects of levamisole such as neutropenia, agranulocytosis and vasculitis, it was largely used in the clinical practice. Originally, due to its immune-stimulant properties, it has been utilized as an anthelmintic agent and in the treatment of some immune-related diseases: recurrent aphthous ulcers (RAU), inflammatory bowel disease (IBD), nephritic syndrome and some dermatologic diseases.¹³

In addition, it has been demonstrated that levamisole causes biochemical alterations, damaging the activity of the brain capillary endothelial cells in the blood–brain barrier^{12–14} and causing several complications, including MIL.¹⁵

However none of the MIL patients having a history of cocaine abuse, pure or contaminated by levamisole, manifested radiological findings mimicking BCS. The only exception was reported by Kocaman et al. They described a case of cocaine-induced MIL mimicking BCS. They

suspected that the toxin was adulterated with levamisole, even if the urine levamisole levels were not tested.¹⁶

Otherwise, a few studies have observed cases of multifocal leukoencephalopathy with predominant ring-type pattern.^{11,17,18} Occasionally, they were strongly suggestive of BCS lesions on MRI-induced by levamisole treatment, suggesting a possible correlation. Long et al.¹⁹ presented a case of leukoencephalopathy, subsequent to therapeutic levamisole administration for ascariasis, which clearly mimicked Balò lesions: concentric ring pattern of iso-hyperintense signal on T1-WI and T2-WI and concentric lamellar enhancement on T1-WI post gadolinium. The levamisole-induced leukoencephalopathy (LILE) was generally depicted on MRI as multiple white matter patchy lesions, hyperintense on T2 and FLAIR sequences, with post-gadolinium enhancement and an abnormal signal on DWI.^{9,18} However, MRI alone not allows to distinguish LILE from MS and its rare variant BCS or from other entities. Therefore, clinical and laboratories data are mandatory; all the patients were responsive to immune-mediated treatments and received steroids or plasmapheresis or immunoglobulin.¹¹

We speculated that our cocaine-addicted patient had developed these cerebral white matter alterations because of the toxic action of cocaine due to metabolic imbalance and mitochondrial dysfunction. Therefore, considering the MRI findings (Balò's-like white matter lesions) and the histopathologic pattern with an inflammatory background, we postulated a possible overlying role of immune-mediated mechanism triggered by levamisole.

Unfortunately, urine levamisole levels were not tested in our patients, and therefore the possibility that levamisole is responsible for their presentation is not proven.

A stereotactic biopsy, executed on the lesions, demonstrated aggregates of reactive astrocytes, perivascular cuffing of small lymphocytes, macrophagic infiltration and relative preservation of axons that seemed to be consistent with a so-called pattern III appearance of BCS (active demyelination with oligodendrocyte apoptosis and preferential loss of the periaxonal myelin components on an inflammatory background).²³

According to this classification, BCS belongs to subtype III, in which the oligodendrocytes are the disease's primary targets by induced apoptosis and loss of MAG (myelin-associated glycoprotein). Astrocytopathy has also been proposed as an associated alteration in BCS.

Due to the limitation of the sample size on biopsy, we did not demonstrate any typical macroscopically ring appearance of the lesions or alternated layers with active demyelination and absent/minimal demyelination.

Primarily, the most challenging aspect of BCS is that its pattern of demyelination resemblances to hypoxia-like tissue injury. Scientific evidences show the local production of oxygen free radicals, cytokines and other neurochemical mediator resulting in destruction of myelin sheaths.²⁴ It is presumed that an impaired activity of the mitochondrial respiratory chain or a microvascular compromise is involved in this damage. All these data suggest that in Baló's sclerosis the rings of demyelination and partial myelination underly an hypoxic-ischemic tissue caused by some unknown agents, like virus or toxins.^{23,25}

Based on the MRI and histological characteristics of the described lesions, one of the most interesting differential diagnoses is ADEM, typically present with fever or a story of infections (not in our patient) and with foci of white matter lesion larger than MS or LILE on MRI.

LILE and ADEM show similar brain pathology, clinical manifestations and radiological findings, even if LILE is rarely associated with fever, myalgia, nausea or other clinical symptoms before the onset of neurological manifestation. On MRI, ADEM showed large white matter lesions involving deeper cortical laminae, thalamus, basal ganglia and brainstem, with no temporal dissemination. On biopsy, ADEM usually demonstrated perivenular foci of demyelination, instead astrocytopathy or hypertrophic astrocytes has been proposed as an hallmark of BSC.^{11,18}

Conclusion

In conclusion, the aim of this study was to broaden current knowledge of a rare and often unrecognized disease like BCS, emphasizing the concomitant history of cocaine-levamisole abuse of the patient. The early diagnosis through MRI findings of BCS is fundamental because several authors have documented good outcomes after administration of corticosteroids

and/or i.v. immunoglobulin and plasmapheresis/plasma exchange. Unfortunately, we have not been able to prove any significant relationship between levamisole and BCS lesions in our patient due to the lack of urine levamisole levels. However, a high correlation possibility still subsists.

It is also possible that cocaine alone may induce Baló's-like lesions without levamisole contamination through immunologic pathways due to altered endothelial function. This can expedite immune cells migration into central nervous system and secretion of pro-inflammatory cytokines.

Declaration of conflicting interests

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Informed consent

Written informed consent was retrospectively obtained from a legally authorized representative for anonymized patient information to be published in this article.

ORCID iD

Daniela Grasso  <https://orcid.org/0000-0003-4876-7780>

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