

# Mitochondrial neurogastrointestinal encephalomyopathy mimicking chronic inflammatory demyelinating polyradiculoneuropathy

Encefalomiopatia neurogastrointestinal mitocondrial mimetizando polirradiculoneuropatia inflamatória desmielinizante crônica

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**Conflict of interest:** There is no conflict of interest to declare.

Received 08 September 2011; Received in final form 14 October 2011; Accepted 21 October 2011

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare multisystemic autosomal recessive disease caused by mutations in the gene encoding thymidine phosphorylase<sup>1</sup>. The deficiency of this enzyme produces plasma accumulations of its substrates, thymidine and deoxyuridine, that have toxic effect on mitochondrial DNA, leading to multiple deletions and depletion. Clinically, the disease is characterized by severe gastrointestinal dysmotility, cachexia, progressive external ophthalmoplegia, peripheral neuropathy and diffuse leukoencephalopathy on brain magnetic resonance imaging. The diagnosis is made by biochemical and molecular tests<sup>2</sup>. New therapeutic approaches remain unproven.

## CASE REPORT

A 36-year-old male patient was referred to our hospital presenting general weakness, muscular atrophy, growth and developmental delay since 6 years old. He also had chronic diarrhea associated to abdominal pain, weight loss, nausea and vomiting<sup>3</sup>.

Cachexia, main muscular groups atrophy and mild palpebral ptosis, associated to ophthalmoparesis were observed. There was symmetrical paresis of both distal and proximal, mainly on the lower limbs and universal areflexia. The sensitive examination revealed distal tactile, thermal and pinprick hypoesthesia.

The electroneuromyography demonstrated demyelinating sensory and motor polyneuropathy, characterized by

conduction slowing and increase latency in motor and sensory nerves and conduction block in 2 motor nerves (Table).

Biochemical tests revealed no thymidine phosphorylase activity and significant increase of serum thymidine and deoxyuridine 9.6 e 8.6 mmol/L, respectively; normal <0.05 mmol/L<sup>3</sup>.

The magnetic resonance imaging (MRI) of the brain showed diffuse leukoencephalopathy affecting both cerebral hemispheres, brain stem and cerebellum.

The muscular biopsy revealed type 2 fibers atrophy and irregular muscle fibers in size and shape. At electronic microscopy, intense mitochondrial proliferation and modest glycogen accumulation were observed<sup>3</sup>.

The superficial fibular nerve biopsy revealed demyelinating pattern with thin myelin to the axonal caliber in different remyelinating stages.

The genetic molecular study detected multiple deletions on mitochondrial DNA. No deletions were identified. Homozygotic mutation was found on exon 10 (C4202A) of the ECGF1 gene<sup>3</sup>.

## DISCUSSION

There were described less than 100 cases of MNGIE over the world on the literature<sup>1</sup>. Despite being clinically recognizable and a homogeneous disease, its presentation form may vary and exhibit atypical phenotypes<sup>1</sup>.

Because it is a rare and recently described disease, many patients are misdiagnosed as myasthenia gravis, chronic

**Table.** Electroneuromyography demonstrating conduction slowing in sensory and motor nerves with conduction block, characterizing a demyelinating pattern.

Nerve	Latency (ms)	Amplitude (mV)	NCV (ms)	Wave F (ms)
Median L	4.2 (n<4) 10.3	7.6 (n>4) 7.6	41.1 (n>52.0)	32.7 (n<33.0)
Ulnar L	3.9 (n<3.7) 9.5 13.8	6.3 (n>4) 4.0 (CB) 3.1	44.1 (n>57) 31.6	41.7 (n<33)
Fibular R	4.8 (n<6.0) 17.4	4.0 (n>2.0) 4.0	31.4 (n>44.0)	41.7 (n<55)
Fibular L	6.2 16.2	5.3 3.6 (CB)	32.2	70.0
Tibial R	4.2 (n<6.7) 20.5	3.0 (n>2) 1.2	31.6 (n>45)	70 (n<57)
Tibial L	7.8 24.1	1.7 0.9	28.3	85.2
Nerve		Latency (ms)		Amplitude (mV)
Sural R		0		
Sural L		0		
Median L		4 (<3.4)		27 (n>15)
Ulnar L		4.3 (n<3.5)		23 (n>10)
Radial L		3.9 (n<3.5)		5 (n>5)

L: left; R: right; NCV: nerve conduction velocity; CB: conduction block; n: normal.

inflammatory demyelinating polyneuropathy (CIDP) and intestinal inflammatory disease<sup>4</sup>. The peripheral neuropathy presented by the patient fulfills the current clinical, electrophysiological and histopathological criteria for CIDP<sup>5</sup>.

In 2004, there were described 5 cases of neuropathy simulating CIDP in patients with MNGIE<sup>4</sup>. Similarities and differences between these two conditions were highlighted. In MNGIE polyneuropathy, proximal weakness is less common than CIDP. Furthermore, there are many other

systemic symptoms associated to this disease. Among the studied cases, none of them obtained clinical improvement with immunomodulating therapy<sup>4</sup>.

The diagnosis of MNGIE was finally confirmed with biochemical analysis demonstrating absence of thymidine phosphorylase activity and serum raise of thymidine and deoxyuridine, in addition to identification of the ECGF1 gene mutation on nuclear DNA and multiple deletions on mitochondrial DNA<sup>3</sup>.

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# Leukoencephalopathy with cerebral calcifications and cyst: Labrune syndrome

## *Leucoencefalopatia com cistos e calcificações cerebrais: síndrome de Labrune*

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**Conflict of interest:** There is no conflict of interest to declare.

Received in 23 August 2011; Received in final form 26 October 2011; Accepted 01 November 2011

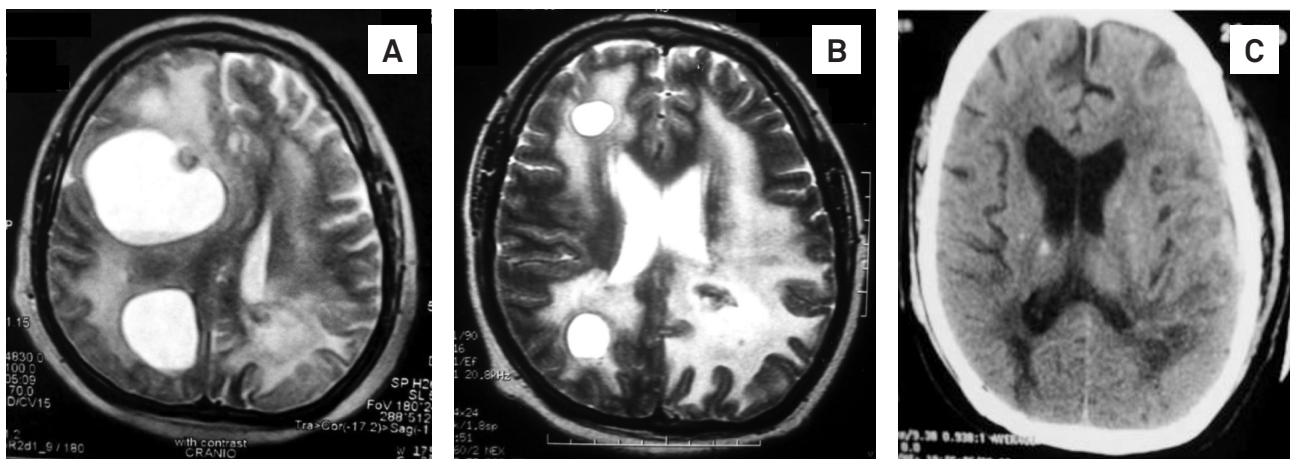
The association of leukoencephalopathy with cerebral calcifications and cysts (LCC), Labrune syndrome is a rare disease, which was first described in 1996<sup>1</sup>. LCC is derived from the syndrome called COATS plus or cerebroretinal microangiopathy with calcifications and brain cysts (CRMCC), reported in 1988. We report a case of an adult patient with LCC.

### CASE REPORT

Patient, male, 31 years-old, son of non-consanguineous parents, and no perinatal complications, he presents a history of tonic-clonic seizures for seven years. Previously healthy, he sought assistance after the first seizure, showing no changes in neurological examination in post-crisis. The patient had complete blood count, renal and hepatic function, glucose, electrolytes, serology for HIV and toxoplasma gondii negative.

Electrocardiogram and cardiac enzymes were normal. In that occasion, the computed tomography (CT) scan showed a bilateral calcification located in the basal ganglia (Fig C). Brain magnetic resonance imaging (MRI) showed extensive area of leukodystrophy and cysts in both hemispheres, the largest measuring 6.7 versus 4.8 cm, with marginal enhancement after intravenous contrast. The repeated MRI showed progression of the lesions (Fig A and B).

In the same month, the largest brain cyst was surgically removed, and the histopathological examination of the cyst showed foci of dystrophic calcifications and focal accumulations of macrophages xanthomized. There were no signs of malignancy in the sample. The patient evolved with partial control of seizures using carbamazepine 1,800 mg/day and he also performed five surgeries to remove brain cysts. Now, the patient is currently with neurological examination demonstrating cognitive syndrome characterized by a transcortical motor aphasia;



**Fig.** (A) Brain MRI showing brain cysts in the right hemisphere with midline shift, compression of the lateral ventricles, and white matter changes; (B) MRI with two brain cysts in the right hemisphere and white matter changes; (C) CT scan showing calcifications in the basal ganglia.

pyramidal syndrome characterized by incomplete hemiparesis on the right hemibody. Myotatic exalted reflexes in the right hemibody and plantar-cutaneous reflex were indifferent.

## DISCUSSION

Reviewing the relevant literature worldwide, Labrune syndrome was considered as a possible diagnosis for the present case<sup>2</sup>. Despite the presence of cysts, calcification, and edema of the white substance found in our patient, suggesting neurocysticercosis, equinecercosis<sup>3</sup> or neoplasia, there was no serologic or histopathologic confirmation.

This syndrome is characterized by calcifications, leukodystrophy, and formation of parenchymal cysts<sup>1</sup>. Its onset can occur during childhood or adolescence, in an average of 12 years (7 months – 59 years), but there was not one in adults in Brazil, with neurological signs such as cognitive decline, seizures and pyramidal, extrapyramidal or cerebellar signs<sup>1,2</sup>. Our patient, unlike the other cases reported in literature,

presented its first neurological manifestation at the age of 24. CT and MRI seen in our case were similar to the cases reported in literature, showing increased signal intensity of the white matter on MRI (T2 and FLAIR), basal ganglia calcification, and development of cysts<sup>1-3</sup>.

Labrune reported the results of histopathology with rearrangement involving the microvessels, whereas perivascular foci of calcifications, hyaline deposits, and formation of Rosenthal fibers seem to be compatible with this change<sup>1</sup>. The histopathological findings of our patient were consistent with LCC. According to them, the likely primary pathologic feature is a rearrangement involving the microvessels and the formation of Rosenthal fibers<sup>1,4</sup>.

In conclusion, the etiology of LCC remains unknown. In spite of relatively characteristic findings in imaging and histopathological examination, there is no uniformity in the clinical findings noted in the published articles. It can be speculated that the later age of onset, normal intelligence and slow progression, like in our patient, may indicate the shape of this rare disease in adults.

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# Metamorphopsia associated with topiramate for migraine prevention

## Metamorfopsia associada ao uso de topiramato para prevenção de enxaqueca

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**Conflict of interest:** There is no conflict of interest to declare.

Received 07 September 2011; Received in final form 02 October 2011; Accepted 10 October 2011

A 33-year-old woman (registration 70-247/ IPUB-UFRJ) has had recurring headaches since the age of 18. She described more right-sided than left-sided throbbing, which could be severe and associated with nausea, light and noise sensitivity, and vomiting. She has had a visual aura, seeing “zig-zags”, lasting for 20 to 30 minutes before

the headaches. The only preventive measure she had taken in the past was divalproex sodium, with good efficacy. Because of the weight gain as a side effect, she refused to take it again. Her body mass index (BMI) was 35.3. She was started on preventive therapy with topiramate at 25 mg daily for two weeks that was to be increased weekly

to 100 mg daily. After 13 days of treatment, she developed continuous visual illusions upon waking in the morning; when looking at human faces, they were distorted and swollen. On many occasions, objects in front of her appeared to be either nearer or farther away. These visual phenomena persisted for approximately 12 hours and gradually disappeared with the discontinuation of topiramate. Thereafter, she never had similar experiences. None of these events was accompanied by the loss of consciousness or headache. The patient's impressions of reality and self-recognition were preserved. The neurological and psychiatric examination was normal, and a complete examination by a neuro-ophthalmologist was normal. An EEG,

with activation procedures (hyperventilation and photic stimulation), and the MRI of the brain were normal.

Metamorphopsia is a visual illusion affecting the perception of the size, shape or inclination of objects<sup>1</sup>. Although this condition occurs in migraine aura, topiramate has been reported to induce other visual illusions, such as palinopsia (the illusion of a persistent or recurrent visual images following the removal of the exciting stimulus)<sup>2</sup> and alterations in body perception ("Alice in Wonderland syndrome") in patients with migraines<sup>3</sup>.

The mechanism by which topiramate may cause these visual illusions in migraineurs is unknown. However, because it may occur in the aura of migraines, these visual illusions are likely to be a result of the migraine.

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# Behavioral changes on amyotrophic lateral sclerosis (ALS): a case of ALS/FTD TDP-43 proteinopathy

Deterioração comportamental na esclerose lateral amiotrófica (ELA): um caso de proteinopatia TDP-43 associada à ELA e demência frontotemporal

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**Conflict of interest:** There is no conflict of interest to declare.

Received 26 June 2011; Received in final form 28 September 2011; Accepted 05 October 2011

The frontotemporal dementia (FTD) is the second most common form of dementia in patients younger than 65 years, and its behavioral variant (bvFTD) is the most prevalent form<sup>1,2</sup>. During the last years, the overlapping between FTD and amyotrophic lateral sclerosis (ALS) has been frequently recognized, with symptoms of FTD preceding ALS and vice-versa. Herein, we report a case of ALS, which afterwards presented psychotic and behavioral symptoms, whose neuropathological diagnosis was compatible with bvFTD-ALS with TAR DNA-binding protein 43 (TDP-43) inclusion<sup>3</sup>.

## CASE REPORT

A 58-year-old man was admitted in our Emergency Unit with a one-year history of progressive weakness of limbs, associated with dysarthria, dysphonia, difficulty to close mouth and hands atrophy. Four days before admission, he developed dyspnea and acute respiratory failure. In the hospital, it was seen generalized weakness, global hyperreflexia, fasciculations on right arm, no sensory abnormalities, and the electroneuromyography showed chronic and acute denervation signs in cranial, cervical

and lumbosacral segments, confirming the diagnosis of amyotrophic lateral sclerosis. As the patient had no social and economic home support, he lived the rest of his life hospitalized, with mechanic ventilation. In the first year after admission, the patient showed anxious and depressive symptoms, associated with a permanent refusal of his condition, with great hopes of cure, even after exhaustive explanation about the diagnosis. This behavior was considered as mechanism of denial.

Progressively, the patient became hostile to nurses and physicians, blaming his disease to clinical staff, with frequent verbal aggression. He said that the family was visiting him, but there were no proof of these visits. After 2 years of hospitalization, the aggressivity worsened, without improvement with antidepressants drugs. The patient affirmed that the disease could be resolved with antibiotic, but the physicians did not want to treat him. In his last months, the persecutory delusions became more intense, associated with visual hallucinations. As there were no clinical signs of delirium, a psychotic delusional disorder was diagnosed and neuroleptic medications were started. His psychiatric status progressively worsened, with auditory hallucinations and physical aggression to the clinical staff. After 2 years and 9 months of hospitalization, the patient died by asphyxia by tracheal blood clot.

On necropsy (Fig), it was seen moderate reduction in hypoglossus nucleus and in anterior column of spinal cord

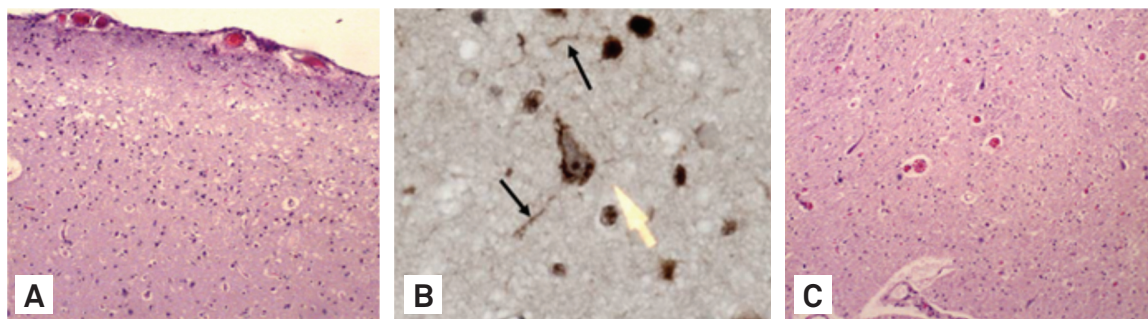
motor neurons, and myelin pallor on anterior and lateral funiculi, sparing posterior funiculus (Fig C), and the brain showed spongiosis in layer II, predominantly in temporal cortex (Fig A and B). The immunoreactivity to protein tau was negative, but there were granular neuronal intracytoplasmic inclusions and dystrophic neurites positive to ubiquitin and TDP-43 (subtype 3 from Mackenzie et al.)<sup>4</sup>.

## DISCUSSION

The discovery of TDP-43<sup>3-5</sup> in brains of patients with the association FTD-ALS has improved the comprehension of its pathophysiology. This specific phenotype often shows the presence of delusions and hallucinations<sup>1</sup>, as seen in our case, and these symptoms should draw our attention to the possibility of TDP-43 proteinopathy on motor neuron disease. As the patient was hospitalized during almost 3 years, it was possible to register details of his behavioral degeneration.

## ACKNOWLEDGMENTS

We thank Dr. Lea Tenenholz Grinberg, MD, PhD, UCSF Memory and Aging Center, USA, for immunohistochemical reaction to TDP-43.



**Fig.** (A) Temporal cortex. Microvacuolization of layer II. Hematoxylin and Eosin, X100. (B) Frontal cortex. Neuronal intracytoplasmic inclusions (yellow arrows) and in dystrophic neurites (black arrows). Immunohistochemistry for TDP-43, X400. (C) Anterior horn of the spinal cord. Marked loss of motor neurons. Hematoxylin and Eosin, X100.

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# Central neurocytoma of spinal cord

## Neurocitoma central da medula espinhal

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**Conflict of interest:** There is no conflict of interest to declare.

Received 02 August 2011; Received in final form 25 August 2011; Accepted 01 September 2011

Spinal cord neoplasms account for 4% of central nervous system (CNS) tumors<sup>1</sup>. Neurocytomas (CN) are neoplasms that occur in the ventricles, being rarely described in the spinal cord<sup>2</sup>. The clinical and neuropathological features of one CN are reported in this article. This is the first description of CN in the spinal cord in Brazil.

### CASE REPORT

A 15-year-old woman had a right hand dysfunction and cervical pain. Magnetic resonance imaging (MRI) showed an intramedullary tumor. During surgery, it was observed a circumscribed lesion at the superior part of the tumor, infiltration in the inferior portion, and a subtotal resection was achieved. Patient kept the same neurological status after surgery.

Histopathological examination revealed sheets of uniform sized cells with small rounded nuclei, finely stippled chromatin, and inconspicuous nucleoli. The cytoplasm was scant, slightly eosinophilic. At some places, tumor cells showed clear perinuclear haloes resembling oligodendroglioma. There were cellular areas alternating with neuropil-like fibrillary matrix, often perivascular in orientation, resulting in a resemblance to ependymoma (Figure).

Immunohistochemical stains were performed and the following antibodies were used: glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), p53 protein, synaptophysin, S100 protein, vimentin, and Ki-67. The immunohistochemical showed strong and diffuse immunostaining for synaptophysin and S100 protein, expression of GFAP, and a high 13% Ki-67 (Figure).

At the ultra-structural level, the neuropil-like matrix was revealed as a web of neuritic processes containing dense-core granules, synaptic vesicles and bundles of microtubules,

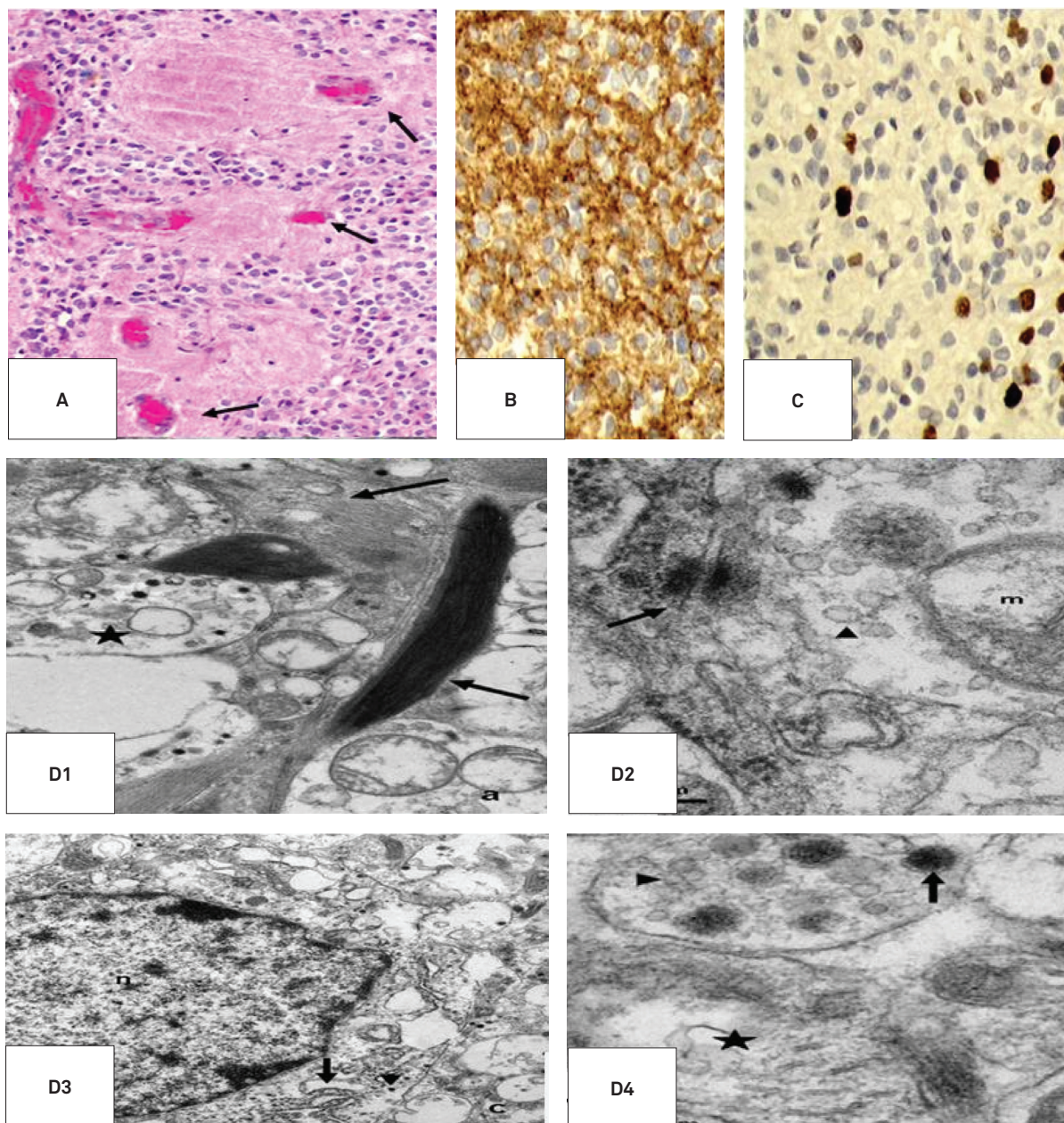
intermingled with astrocytic processes. Some synaptic junctions were also found. Cell bodies presented a round nucleus, with loose chromatin, and a scanty cytoplasm, with an evident granular endoplasmic reticulum, Golgi complex, microtubules, and some dense-core granules (Figure). These morphological and immunohistochemical findings indicate a neuronal differentiation, which is consistent with the diagnosis of CN.

### DISCUSSION

The World Health Organization (WHO) classification of CNS tumors includes CN since 1982<sup>2</sup>.

The differential diagnosis of CN includes oligodendroglioma and ependymoma<sup>2,3</sup>. The distinction from oligodendroglioma can only be made by immunohistochemical and ultra-structural evidence of neuronal origin seen in CN<sup>4</sup>. Ependymomas have a coarser glial fibrillary matrix, instead of the fine neuropil-like fibrillary matrix of CN. Their cells exhibit more angulated nuclei, they are negative for synaptophysin and show at ultra-structural level true or intracytoplasmic lumens decorated by microvilli and cilia, which were not found in this case<sup>2,4</sup>. The occurrence of astrocytic differentiation is well documented in CN, especially for extraventricular<sup>2,4</sup>. This was observed in the present case in the form of GFAP and S-100 protein expression and astrocytic processes<sup>4</sup>. The only feature observed that can be associated with an aggressive behavior was a high Ki-67 index<sup>3-5</sup>. Despite the absence of anaplastic features, labeling proliferative index in more than 2% is considered as this case atypical, according to Sharma et al.<sup>5</sup>.

This letter describes the tenth case of extraventricular CN on the spinal cord and is the first description of this tumor in Brazil.



**Figure.** (A) Histopathology. Fibrillary matrix, perivascular in orientation (arrows), resembling perivascular pseudorosettes of ependymoma. (B) Immunohistochemistry. Strong and diffuse immunostaining for synaptophysin, indicating a neuronal differentiation. (C) High Ki-67. (D) Transmission of electron micrographs. (D1) Neuropil presenting neuritic processes containing dense-core granules (star) and astrocytic processes (arrows). (D2) Neuritic process presenting a synaptic junction (arrow), synaptic vesicles (arrowhead), and mitochondria (m). (D3) Cell body presenting a round nucleus (n), granular endoplasmic reticulum (arrow), and scattered dense-core granules (arrowhead). (D4) Detail of a neuritic process rich in microtubules (star) and another with dense-core granules (arrow) and synaptic vesicles (arrowhead).

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