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Balo's concentric sclerosis: a clinical case

This paper describes a case of Balo's concentric sclerosis, a rare demyelinating disease of the central nervous system (CNS), which is currently classified as multiple sclerosis. In recent years, there has been a more favorable clinical course of Balo's sclerosis. The significant polymorphism of clinical manifestations of the disease, its neuroimaging pattern, and laboratory tests cause difficulties diagnosing this pathology. Its differentiation with CNS tumors presents a particular challenge. So it also happens in the described clinical case, when computed tomography revealed the signs of space-occupying lesion, the histological pattern of concentric focus biopsy specimen indicated the presence of protoplasmic astrocytoma. However, immunohistochemical analyses of the biopsy specimen, immunological examination of cerebrospinal fluid, as well as the typical magnetic resonance imaging changes of Balo's sclerosis could suggest the demyelinating nature of the pathological process. The article shows that immunohistochemical techniques for examining a brain biopsy specimen and immunological assays of blood and cerebrospinal fluid are of great diagnostic value.

Keywords: *concentric sclerosis; Balo's disease; demyelinating disease; multiple sclerosis; neurohistology; immune histochemistry.*
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In 1928, the Hungarian pathologist Jozsef Balo described for the first time a demyelinating disease of the central nervous system characterized by concentric areas of tissue destruction developing in some parts of the white matter of the brain [1]. In the case report presented by this author, a young man's handwriting deteriorated as he was unable to write certain letters, he also presented with speech retardation and impairment of fine motor skills and spatial perception (difficulty in using fork and knife during meals, as well as impaired perception of their location on the table). Physical examination revealed a mildly elevated body temperature (to 37.3 °C), right-sided facial palsy, no pharyngeal reflex and no superficial abdominal reflexes on the right. Notably, the cerebrospinal fluid (CSF) sample tested positive in Pandy's reaction (+). Six days later the patient was discharged and advised to continue iodine therapy in an outpatient setting. Three days after the discharge, the patient developed a right-sided hemiparesis that worsened over the next 3 days to the level of plegia; he then started experiencing headache, nausea, and vomiting as well. The patient was treated by therapeutic phlebotomy and blood-letting, electrical stimulation, and light therapy using a quartz lamp. This treatment produced an improvement: movements were regained in the paralyzed limbs. Ten days later, the patient's condition significantly worsened again, as he had impaired urination, trismus, tonic contractions of the muscles of the right extremities, and marked weakness. A re-examination revealed a subfebrile body temperature (up to 37.5 °C). Urinary and faecal incontinence occurred. Neurological examination demonstrated a right-sided facial palsy of central origin, hyperactive patellar and ankle jerk reflexes, hyperactive reflexes in the right extremities (ankle jerk to the level of clonus), disappearance of the abdominal reflexes, and a muscle tone increase of central origin in the right extremities. The pathological Babinski sign was positive on the right. The pathological Kernig's and Trousseau's signs were also positive. Total aphasia was observed. Optic fundus examination revealed bilateral optic neuritis. In a follow-up cerebrospinal fluid test, Pandy's reaction was negative. The severe focal symptoms led to a suspected diagnosis of a space-occupying lesion in the frontal lobe involving Broca's area.

The condition kept deteriorating over the next 3 days, leading to a fatal outcome. Post-mortem examination demonstrated a circumscribed concentric focus of demyelination in the white matter of the left hemisphere. After that, approximately 100 more reports were published of similar morphological manifestations observed either on post-mortem examination or, in later years, in patients undergoing magnetic resonance imaging (MRI) of the brain. These studies did not find any relevant changes in clinical or biochemical CSF tests. The general view is that this condition is made specific not only by the typical geometrical form of demyelinated lesions, but also by the characteristic pathomorphological findings, with concentric areas of remyelination and without damage to the axial cylinders.

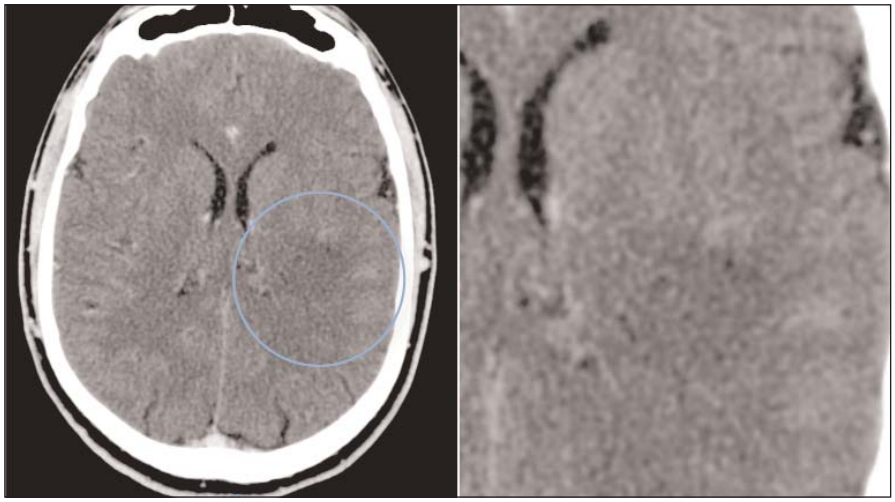

Figure 1. *CT of the head with a hypodense lesion in the left parietal lobe*

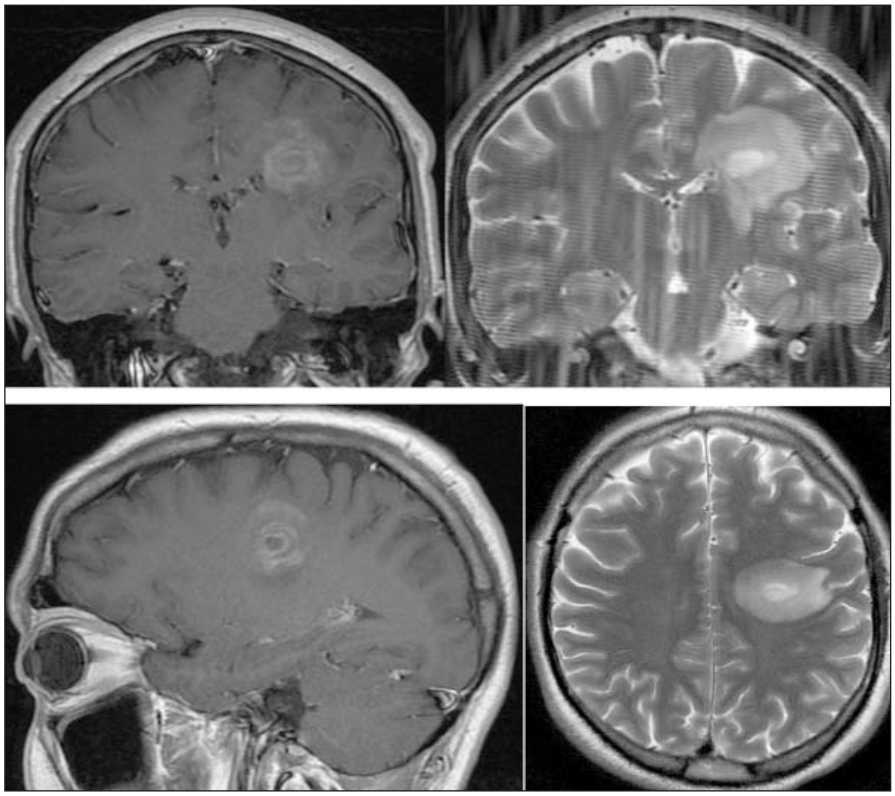

Figure 2. *Multiple small cysts and hemorrhage, a site of necrosis. Haematoxylin-eosin i40.*

A number of theories of the pathogenesis of Balo concentric sclerosis (BCS) were proposed afterwards, including those of concentric remyelination, distal oligodendrogliopathy, astrocytopathy, as well as a colloid theory [2]. None of these theories has been fully confirmed to date; however, the disease itself is an atypical form of multiple sclerosis, as initially thought by J. Balo and in contrast to an initial conception of this pathological process as a periaxial leukoencephalitis [3]. The development of this atypical clinical variant of multiple sclerosis has been shown to have some specifics. A high mortality rate was reported in some case reports, while others describe a benign disease [3, 4]. In this paper, we present a case of a benign variant of Balo concentric sclerosis in a patient who was treated at the Neurology Clinic of the S. M. Kirov Military Medical Academy in 2017.

Case Description

Patient Ch., male, 29 years old, *private entrepreneur, had no chronic or hereditary diseases and an uncomplicated medical history. As the patient was working on his computer at night on 28 June 2017, approximately at 2 a.m., before going to bed, with no preceding symptoms, he experienced numbness in the right side of the body, weakness and impaired coordination in the right extremities. After waking up at approximately 8 a.m., he still felt weakness and numbness in the right extremities. The patient's relations noticed that his speech had changed and become slurred. He was brought as an emergency case to a regional vascular centre, where computed tomography (CT) of the head demonstrated a hypodense lesion in the left parietal lobe (Figure 1). Cerebral CT angiography revealed no disorders indicative of an ongoing vascular disease, and the patient was admitted to a neurosurgery department for a suspected space-occupying lesion.*

Over the next 3 days, the patient experienced weakness in the right extremities that worsened to the level of plegia, as well as hypoaesthesia in the right extremities; he was unable to move on his own. Dexamethasone 12 mg/day with saline was administered by intravenous drip for 10 days. This was followed by an improvement: increased muscle strength and improved sensation.

On 05 July 2017, he had an MRI of the head with intravenous contrast enhancement (Figure 2). MRI revealed a solitary, large, T2 hyperintense lesion in the left parietal region, which was unevenly contrast-enhanced, thus ruling out an acute cerebral vascular accident. CSF examination: cell count 18 cells per μL, positive Pandy's reaction, protein 0.33 g/L, no tumour cells. Stereotactic biopsy of the brain in the region of the T2 hyperintense lesion and subsequent histological examination were performed to rule out a space-occupying lesion (Figures 3, 4).

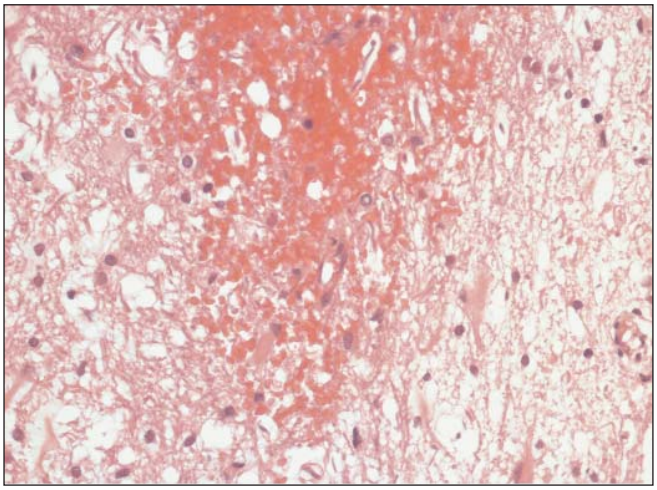

Figure 3. *Drainage astrocytes, blood vessel containing neutrophils, a site of necrosis. Haematoxylin-eosin i40.*

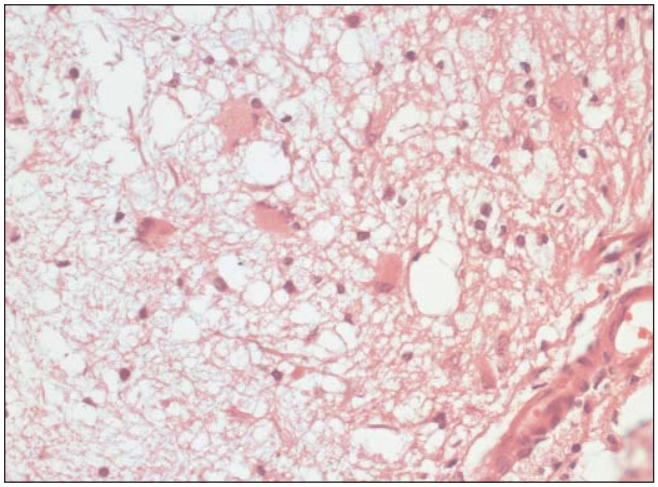

Figure 5. *Multinuclear astrocytes, moderately expressed demyelination in area of elective necrosis.*

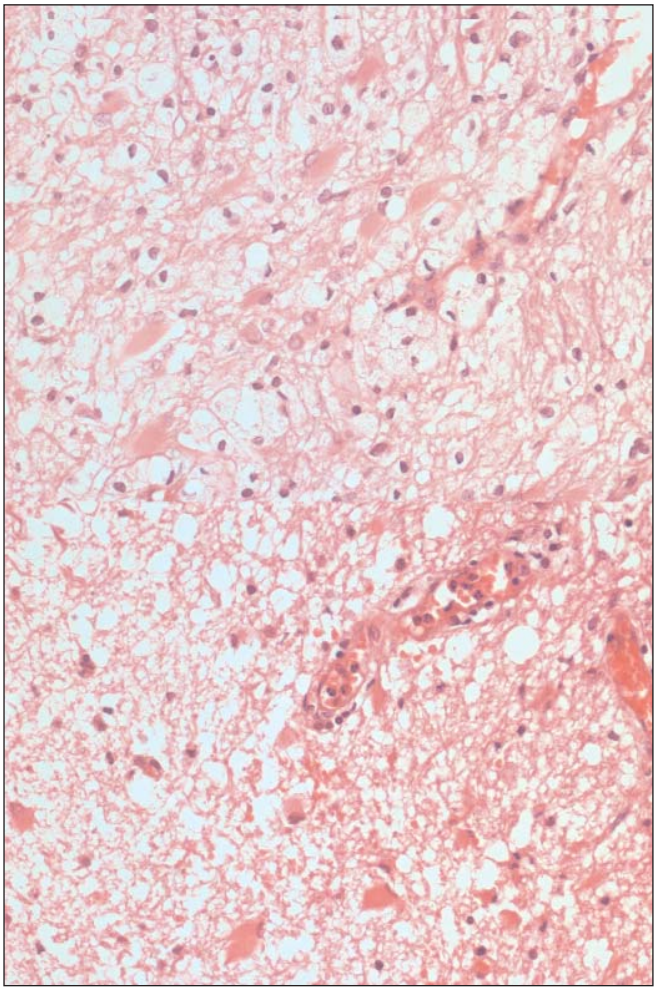

Figure 4. *T1W and T2W MRI shows concentric focus of lesion of the brain with limited edema zone. 05 July 2017.*

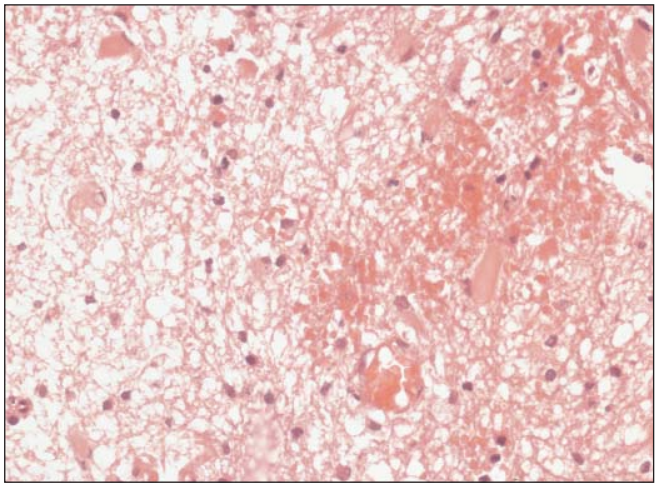

Figure 6. *Site of necrosis and the foci of hemorrhage. Haematoxylin-eosin i40.*

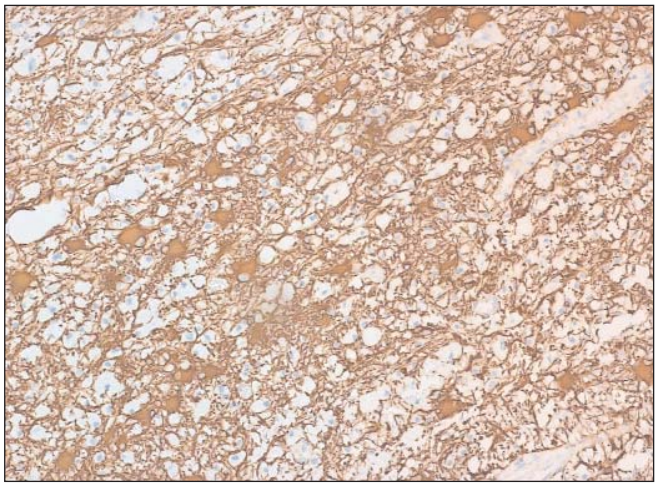

Figure 7. *Expression of glial acidic protein in reactive astrocytes.*

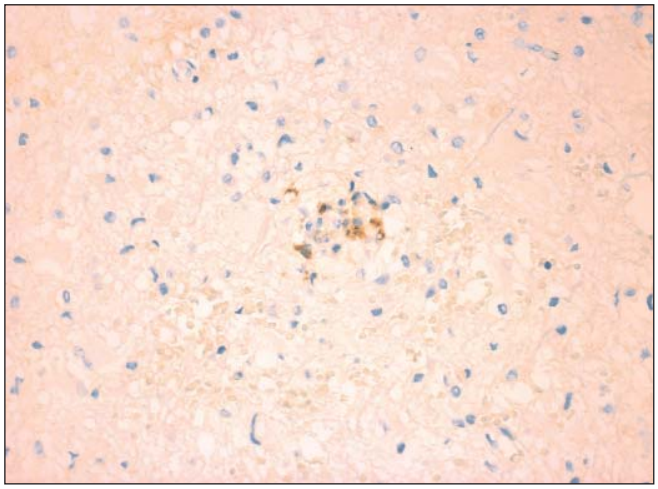

Figure 8. *Diffuse CD-45 expression.*

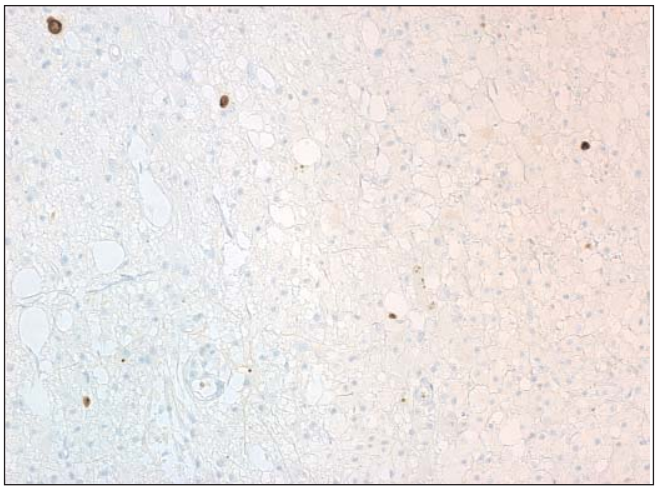

Figure 10. *Ki-67 up to 2 %.*

Microscopy findings: the brain matter contains a tumour consisting of numerous monomorphic astrocytes with a wide, clear cytoplasm and a clear nucleus displaced to the periphery. Multiple small cysts. Small haemorrhages. Conclusions: protoplasmic astrocytoma.

Therefore, the obtained test results provided contradictory information on the nature of the pathological process. After the biopsy, as a favourable effect of the administered conservative therapy was still observed and no convincing clinical evidence indicative of a brain tumour was available, the patient was discharged from the neurosurgery hospital to be followed up afterwards; a diagnosis of "an intracerebral space-occupying lesion in the left frontoparietal region" was made.

After that, in December 2017, as the complaints and the neurological deficit persisted (mild weakness in the right extremities, mild speech impairment – inability to pronounce certain sounds, tremor in the right hand) and a final diagnosis had been made, the patient was admitted to the Neurology Clinic of the Military Medical Academy. On physical examination, the somatic status was unremarkable. On neurological

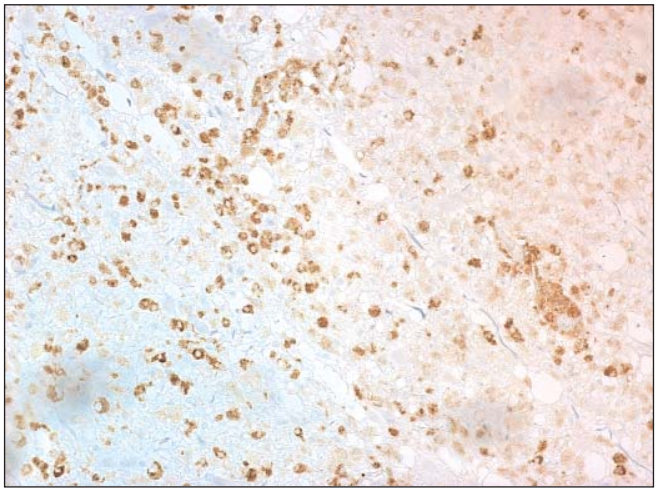

Figure 9. *Total CD-68 expression in macrophages.*

examination, findings included a fine horizontal nystagmus on lateral gaze and elements of motor aphasia in speech. Limb muscle strength was satisfactory, right < left. A muscle tone increase of central origin was observed in the right extremities. The superficial abdominal reflexes were hypoactive and symmetrical. Deep tendon reflexes in the extremities were hyperactive, right > left, with clonus of the right foot. A positive pathological pyramidal Rossolimo's hand sign on the right, with no pathological pyramidal signs in the feet. Tests of coordination (finger-nose, finger-hammer, heel-knee) were performed with intentional tremor and past-pointing to the right. The patient presented with a central-type pelvic function disorder (complained of urinary urgency). The MR images presented by the patient demonstrated a large, T2 hyperintense lesion in the left parietal region that had a concentric structure, which led to a preliminary diagnosis of Balo concentric sclerosis.

A lumbar puncture was carried out to confirm the diagnosis, and produced a clear, colourless cerebrospinal fluid and a CSF pressure of 105 mm H2O; the cerebrospinal fluid pathways were patent, cell count: 6.0×10^6/L – lymphocytes, protein 0.484 g/L, glucose 3.59 mmol/L. A complex multiple sclerosis test revealed elevated cerebrospinal fluid level of immunoglobulin free light chains kappa >2.5 (reference interval 0–0.5 μg/mL) and immunoglobulin free light chains lambda 0.03 (reference interval 0–0.1 μg/mL), oligoclonal IgG bands in the cerebrospinal fluid (OCB+) and polyclonal IgG in the serum (synthesis type 2). A visual evoked potential test revealed signs of a severe impairment of visual sensory input on the right, with equal involvement of the macular and peripheral regions in the pathological process. A repeated, more detailed assessment of the biopsy material was performed (Figure 5, 6).

Immunohistochemical examination of the biopsy material demonstrated a positive expression of glial acidic protein in reactive astrocytes (Figure 7). Negative expression of IDH1 R132H (isocitrate dehydrogenase). Diffuse CD-45 expression in few cells (Figure 8). Total CD-68 expression in macrophages (Figure 9). Ki-67 up to 2 %

Figure 11. *Histological findings obtained by J.Balo: alternation of sites of inflammation, necrosis, demyelination and hemorrhage with a relatively preserved tissue of the brain.*

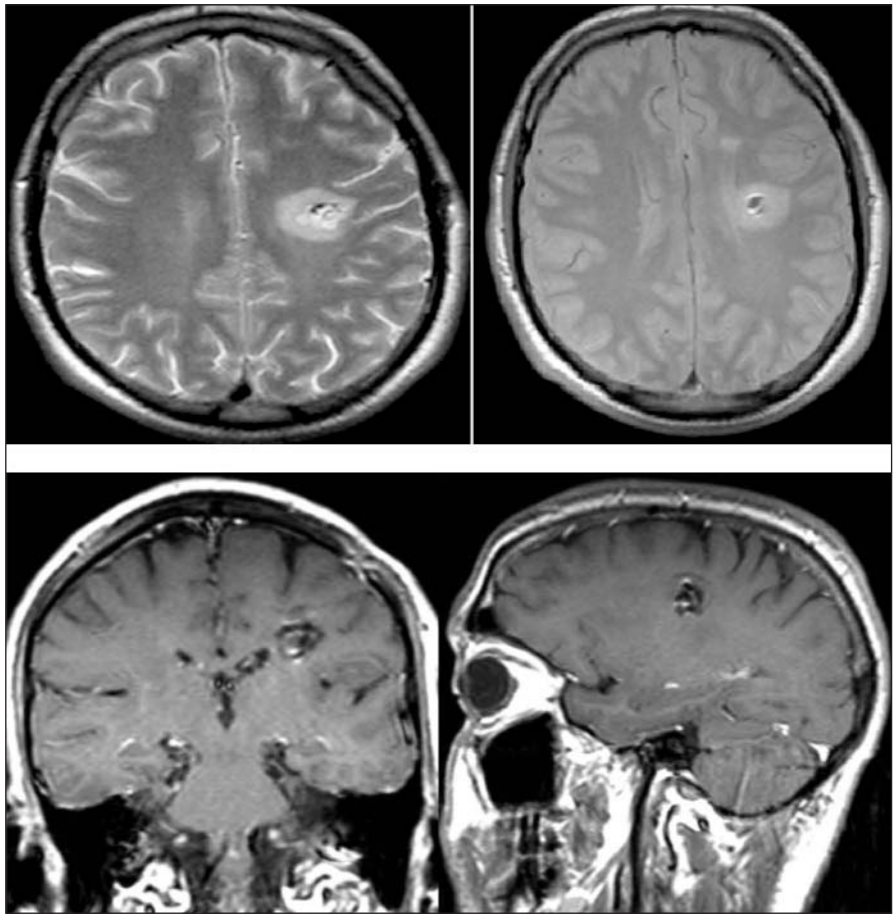

Figure 12. *MRI of the head 06 December 2017. Structural and post-biopsy changes in the substance of the brain.*

(Figure 10). Conclusion: no convincing evidence of a neoplastic process, the morphological findings and immunophenotype are rather indicative of a demyelinating disease.

Therefore, this analysis of the neuromorphological changes in the lesion demonstrated no signs of tumour-associated damage to the brain matter [5, 6]. Alternating areas of necrosis, inflammation, and decreased neuropil volume, as well as demyelination with areas of comparatively preserved brain matter, were observed. The immunohistochemical examination confirmed the absence of any signs of a neoplasm in the central nervous system. The histological findings on light microscopy correspond to the data published by J. Balo in 1927 (Figure 11):

Follow-up MRI in December 2017 (Figure 12). Evidence of an area of structural changes in the brain matter at the border of the left frontal and parietal lobes (with post-biopsy changes in the central regions) and a focus of gliosis in the left frontal lobe. Combined with the biopsy data, this evidence most probably indicates a demyelinating disease. MR evidence of structural changes in the left corticospinal tract most likely indicative of developing Wallerian degeneration. Compared with the data obtained on 05 July 2017: a small reduction in the dimensions of the area of gliosis at the border of the left frontal and parietal lobes.

Conclusions. *This case report demonstrates that, notwithstanding the considerable progress in neuroimaging, immunological diagnostics, and functional tests, differential diagnosis between tumours and some rare demyelinating diseases is still associated with significant difficulties encountered by specialists [7–11]. Standard histological examination does not always allow a final diagnosis either, which necessitates the use of the most sensitive immunohistochemical techniques.*

Our analysis of the cases of Balo concentric sclerosis presented above revealed a trend towards more favourable (benign) course of the disease and fewer fatal outcomes in recent years. These findings may be due to changes in the immunological responsiveness of the population, as well as the more frequent and more active use of glucocorticoid therapy, which certainly warrants further investigation.

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