

Encephalomyelitis associated with rheumatoid arthritis: a case report

Albert Acewicz¹, Teresa Wierzba-Bobrowicz¹, Łukasz Michałowski^{2,3}, Mariola Pęczak⁴, Sylwia Tarka^{1,5}, Dominik Chutorński¹, Tomasz Stępień¹, Paulina Felczak¹, Katarzyna Sklinda⁶, Anna Nasierowska-Guttmejer^{2,7}, Małgorzata Dorobek⁴

¹Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland, ²Department of Pathology, Central Clinical Hospital of the Ministry of the Interior and Administration, Warsaw, Poland, ³Department of Pathology, Medical University of Warsaw, Warsaw, Poland, ⁴Department of Neurology, Central Clinical Hospital of the Ministry of the Interior and Administration, Warsaw, Poland, ⁵Department of Forensic Medicine, Medical University of Warsaw, Warsaw, Poland, ⁶Department of Radiology, Centre of Postgraduate Medical Education, Warsaw, Poland, ⁷Faculty of Medicine, Lazarski University, Warsaw, Poland

Folia Neuropathol 2021; 59 (1): 91-97

DOI: <https://doi.org/10.5114/fn.2021.103805>

Abstract

Encephalitis/encephalomyelitis in the course of rheumatoid arthritis (RA) remains a matter of debate. We present a case of a patient with encephalomyelitis associated with RA confirmed with post-mortem neuropathological examination. A 68-year-old woman with a long-standing, seropositive history of RA presented progressive disturbances of consciousness. Magnetic resonance imaging (MRI) of the brain and cervical spine revealed an increase of signal intensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) images with corresponding restricted diffusion involving cerebral peduncles, pons, medulla oblongata, and cervical spinal cord and mild contrast-enhancement of the right cerebral peduncle. Extensive radiological and laboratory testing, including autoantibodies to paraneoplastic anti-neuronal and neuronal cell surface antigens, were all negative except for elevated rheumatoid factor. Cerebrospinal fluid (CSF) analysis revealed moderate pleocytosis with mononuclear cell predominance, mildly increased protein level, and negative viral PCRs, bacterial cultures, flow cytometry, and neuronal surface antibodies. Despite intensive treatment with corticosteroids, antibiotics, antiviral drugs, and intravenous immunoglobulin the patient died after 3 months of hospitalization. Post-mortem neuropathological examination revealed numerous, disseminated, heterochronous ischaemic lesions, rarely with haemorrhagic transformation, predominantly in the brainstem, and widespread, diffuse microglia and T-cell infiltrations with neuronal loss and astrogliosis, most severe in the frontal and temporal lobes. Mild, perivascular lymphocyte T infiltrations involved particularly small and medium-sized vessels and were associated with brainstem ischaemic lesions. The neuropathological picture confirmed diagnosis of encephalomyelitis, which together with the clinical course suggested association with RA. Concluding, encephalomyelitis due to RA remains a challenging, controversial entity that needs further research and the establishment of effective diagnostic and treatment guidelines.

Key words: encephalomyelitis, rheumatoid arthritis, neuropathology, encephalitis, vasculitis.

Communicating author

Albert Acewicz, MD, PhD, Department of Neuropathology, Institute of Psychiatry and Neurology, 9 Sobieskiego St., 02-957 Warsaw, Poland, e-mail: aacewicz@ipin.edu.pl

Introduction

Rheumatoid arthritis (RA) is a common, chronic, progressive connective tissue disease in which joints are the primary target. Extra-articular manifestations include skin, eye, lungs, and blood vessels [10]. Although the central nervous system (CNS) is rarely involved, a variety of neurological manifestations can occur associated with vasculitis, pachymeningitis, meningitis, opportunistic infection, drug adverse effects, and spinal cord compression [3,4,11,12].

Encephalitis in the course of RA remains a matter of debate. Critics suggest other causes of encephalitis in RA patients, or associate brain damage symptoms with vasculitis. To the best of our knowledge, there is a single clinical report in the literature of encephalitis due to RA. Kitamura *et al.* [7] described a 57-year-old patient with autoimmune encephalitis (AE) associated with preclinical stage of RA with extensive, symmetric parenchymal changes involving the medial temporal lobes in brain magnetic resonance imaging (MRI) and no autoantibodies to neuronal intracellular or cell-surface antigens in either the serum or cerebrospinal fluid (CSF). In conclusion, the authors suggested that AE can develop as an extra-articular manifestation of RA, in opposition to the published diagnostic criteria of AE, in which rheumatological disorders were listed in the differential diagnosis [5].

The diagnosis of AE associated with RA in the paper of Kitamura *et al.* [7] was based on clinical, laboratory, and radiological findings. Although, it is of interest whether brain changes correspond with the diagnosis of encephalitis in the neuropathological examination. Here, we present a case of a patient with encephalomyelitis associated with RA confirmed with post-mortem neuropathological findings. To the best of our knowledge, it is the first study with a description of pathological changes in the literature.

Case presentation

A 68-year-old woman presented transient fever, weakness, dizziness, imbalance, nausea, disorientation, and somnolence, which progressed for 2 weeks. She had a history of long-standing, seropositive RA with no extra-articular manifestations controlled by chronic glucocorticosteroid (GKS) therapy, secondary hypoadrenocorticism, hypertension, osteoporosis, stomach ulcers, total hysterectomy with bilateral salpingo-oophorectomy and chemotherapy due to

uterine cancer 5 years earlier. In the last few years, she had been hospitalized due to severe electrolyte disturbances several times.

On admission she was confused but able to answer simple questions and perform simple commands, her body temperature and other vital signs were normal, she was dehydrated with no other systemic physical examination abnormalities, no meningeal irritation, and no other focal neurological signs. Routine blood tests revealed hyponatraemia (122 mmol/l, N: 135-145 mmol/l), hypo-osmolality (256 mOsm/kg, N: 270-300 mOsm/kg), leukocytosis (21 cells/ μ l, N: 4-10 cells/ μ l), elevated C-reactive protein (CRP) (111 mg/l, N: < 5 mg/l), and elevated erythrocyte sedimentation rate (ESR) (37 mm/h, N: < 20 mm/h). Results of chest radiography and urine analysis were normal. Despite the correction of electrolyte disturbances and decrease of inflammatory parameters after empirical antibiotic treatment (cefuroxime), her neurological status slowly worsened with further deterioration of her consciousness level; she became somnolent, responding only to painful stimuli. MRI of the brain and spinal cord revealed an increase of signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with corresponding restricted diffusion involving both cerebral peduncles, pons, medulla oblongata, and cervical spinal cord and mild contrast-enhancement of the right cerebral peduncle (Fig. 1). There were no vascular abnormalities in brain magnetic resonance angiography (MRA). Electroencephalography (EEG) showed diffused, generalized slowing with no evidence of abnormal paroxysmal activity. Computed tomography (CT) of the chest, abdomen, and pelvis revealed no significant abnormalities. Blood testing, including routine blood tests, blood glucose, blood lipids, hepatic, renal, adrenal gland, thyroid function, serology, serum electrolytes, coagulation studies, HIV antibodies, hepatitis B and C, syphilis serology, tumour markers, *Borrelia* antibodies, autoimmune antibodies (anti-nuclear antibodies – ANA, anti-neutrophil cytoplasmic antibodies – ANCA, rheumatoid factor – RF, cyclic citrullinated peptide – CCP, LA, cardiolipin), neuronal cell surface autoantibodies (anti-NMDA, anti-LGI1, anti-CASPR2, anti-GABAB, anti-AMPA1, anti-AMPA2, anti-DPPX), and onconeural antibodies (anti-Hu, anti-Ri, anti-Yo, anti-MA2, anti-CV2, anti-amphiphysin, anti-GAD56, anti-SOX1, anti-Zic4), were all negative except elevated rheumatoid factor (25.5 IU/ml, N: < 12.5 IU/ml). CSF analysis revealed moderate pleocytosis (68 cells/ μ l, N: < 5 cells/ μ l) with mononuclear cell predominance

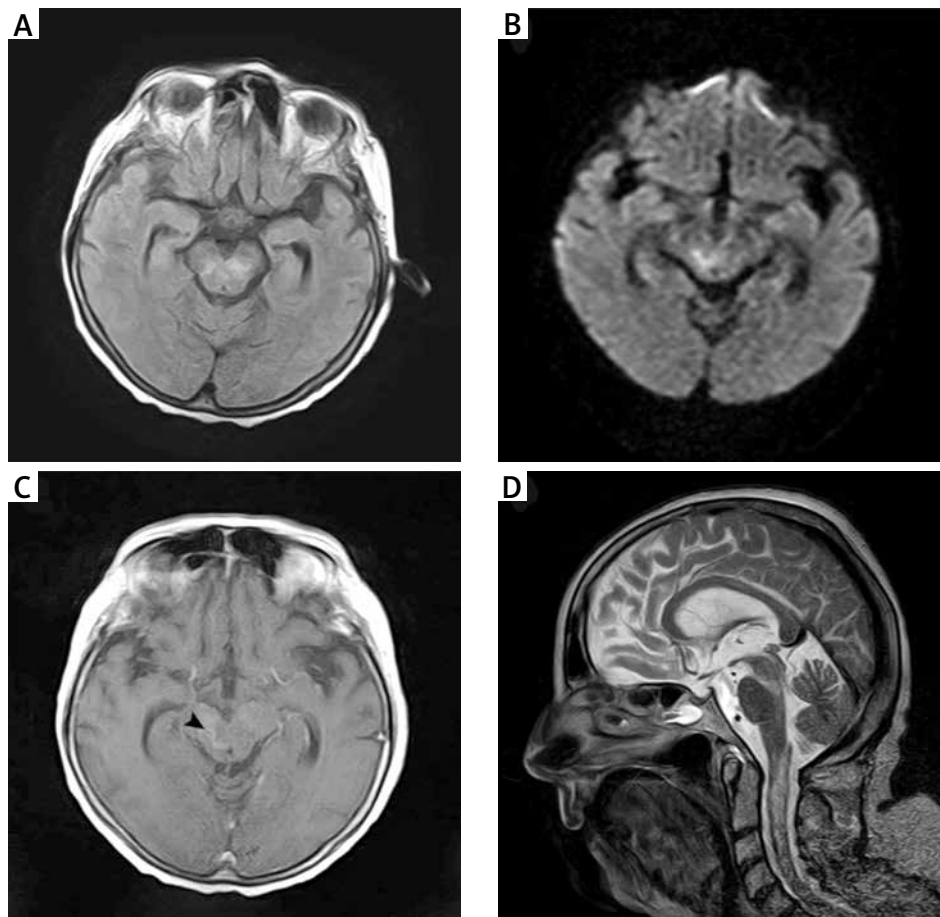


Fig. 1. MRI findings. **A)** Fluid attenuated inversion recovery (FLAIR) hyperintensity in the cerebral peduncles. **B)** Mild diffusion restriction in the cerebral peduncles. **C)** Mild right cerebral peduncle contrast-enhancement (arrowhead). **D)** T2 hyperintensity in the cervical spinal cord.

(92%), mildly increased protein level (48 mg/dl, N: < 45 mg/dl), and a normal glucose level. CSF flow cytometry analysis, 14-3-3 protein testing, viral PCRs (varicella-zoster virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus), and neuronal surface antibodies tests were negative. Results of blood, CSF, and urine bacterial, fungi, and mycobacterium cultures were also negative.

The patient was treated with corticosteroids (methylprednisolone, prednisolone), antibiotics (ceftazidime, metronidazole, imipenem/cilastatin), antiviral drugs (aciclovir), and intravenous immunoglobulin (IVIg) with no improvement. During several weeks of hospitalization her general and neurological condition gradually deteriorated; she became unconscious, unresponsive, hypotensive, and finally ventilatory failure. Several serious complications occurred, i.e. urinary tract infection, *Clostridium difficile* infection,

Pseudomonas aeruginosa sepsis, and epileptic seizures. She needed mechanical ventilation, vasopressors, blood transfusions, broad antibiotics therapy, enteral and parenteral nutrition, and antiepileptic drugs. Her follow-up brain MRI did not show significant progression, CSF analysis revealed slightly decreased pleocytosis (42 cells/ μ l). The patient died after 3 months of hospitalization. A clinical diagnosis of vasculitis due to infection or neoplastic disease was established.

General autopsy revealed right lung haemorrhagic infarct, single renal cysts, mild atherosclerosis, and small articular deformities with no evidence of tumour or systemic vasculitis. The fresh brain weighed 1060 g. Its gross examination disclosed generalized mild atrophy manifested by small brain size, widening of the sulci, narrowing of the gyri, and symmetrical dilation of the lateral ventricles. Small,

multiple, subdural, confluent petechial haemorrhage in the occipital cortex and left occipital gyrus, small cavities in the basal ganglia, and minimal atherosclerosis were observed. The cervical spinal cord did not show any abnormalities in macroscopic evaluation. The leptomeninges were clear.

Formalin-fixed, paraffin-embedded tissue sections were stained histologically (haematoxylin and eosin [HE], Mallory's trichrome, Van Gieson, Gomori trichrome) and immunohistochemically with antibodies for GFAP (1 : 500, Bio-Rad, Hercules, USA), CD20 (1 : 100, Leica, Newcastle, UK), CD34 (1 : 50, Dako, Glostrup, Denmark), CD45RO (1 : 500, Leica, Newcastle, UK), CD68 (1 : 250, Cell Marque, Rocklin, USA), and LCA (1 : 75, Cell Marque, Rocklin, USA). In all examined brain and cervical spinal cord structures mild oedema of the cortex and white matter, congestion of small cortical vessels, diffuse microglia and lymphocytic infiltration, and mild inflammation changes of meningeal and parenchymal small vessels (arterioles, capillaries, and to a lesser extent venules) was observed (Figs. 2 and 3). Parenchymal inflammation was most severe in the frontal and temporal lobes and was accompanied by significant neuronal loss, severe cortex and white matter oedema, perineuronal

satellitosis, numerous hyaline bodies, diffuse astroglial proliferation, and oligodendrocyte swelling (Fig. 2). Microglia was sometimes rod-shaped, sometimes forming nodules (Fig. 2A, B). Lymphocytic infiltration was composed of T-cells, particularly seen in the parenchyma, and rarely associated with vessels (Fig. 2C). The vasculitis showed transmural and perivascular lymphocyte T-cell infiltration with fibrous proliferation of the intima and narrowing of the lumen (Fig. 3). More severe inflammatory vascular changes were observed in the brainstem, cerebellum, and cervical spinal cord and corresponded with multiple, small, or single larger foci of ischaemic necrosis in various pathological stages, predominantly in the final stage of macrophage demolition or glial scar formation (Fig. 3). In the pons, larger foci of ischaemic necrosis were visible, surrounded by a glial shaft composed of proliferative, reactive astrocytes and macrophages (Fig. 3C). There was a larger focus of ischaemic necrosis in the phase of glial scar formation with secondary haemorrhagic features in the cortex and white matter of the right occipital lobe (Fig. 3D). Furthermore, slightly expanded perivascular spaces were seen in the basal ganglia and thinning of the ganglion layer with Bergman glia proliferation in the cerebellum.

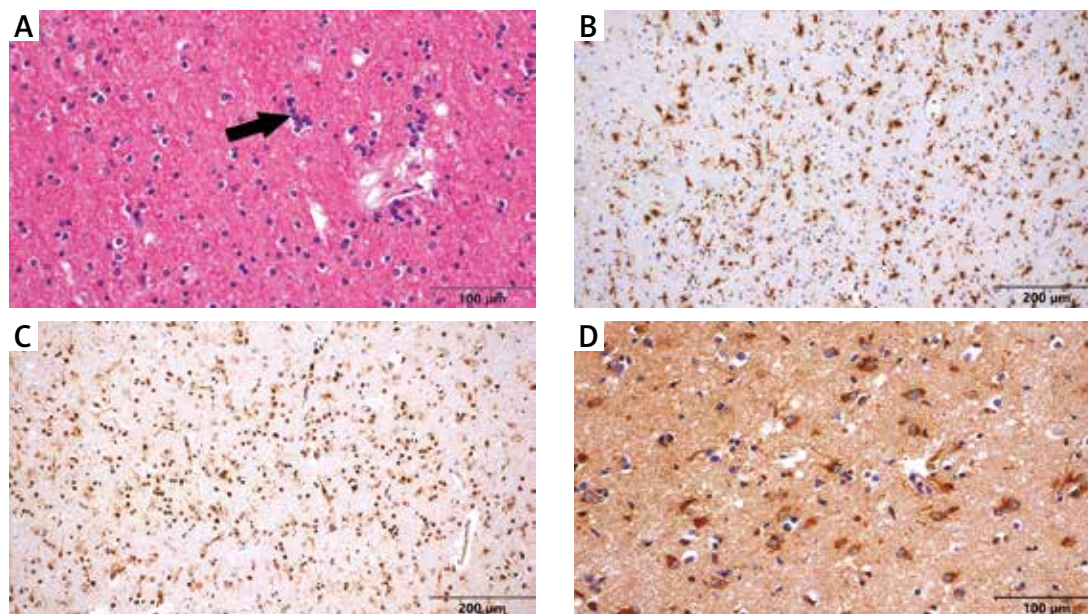


Fig. 2. Microscopic findings. **A)** HE staining of the left frontal lobe reveals diffuse inflammatory infiltrate with microglia/lymphocytic nodules (arrow). **B)** CD68 immunohistochemistry of the left temporal lobe shows microglia/macrophage infiltration. **C)** CD45RO immunohistochemistry of the left temporal lobe discloses parenchymal inflammation composed of lymphocyte T. **D)** GFAP immunohistochemistry of the left frontal lobe reveals astrocyte proliferation.

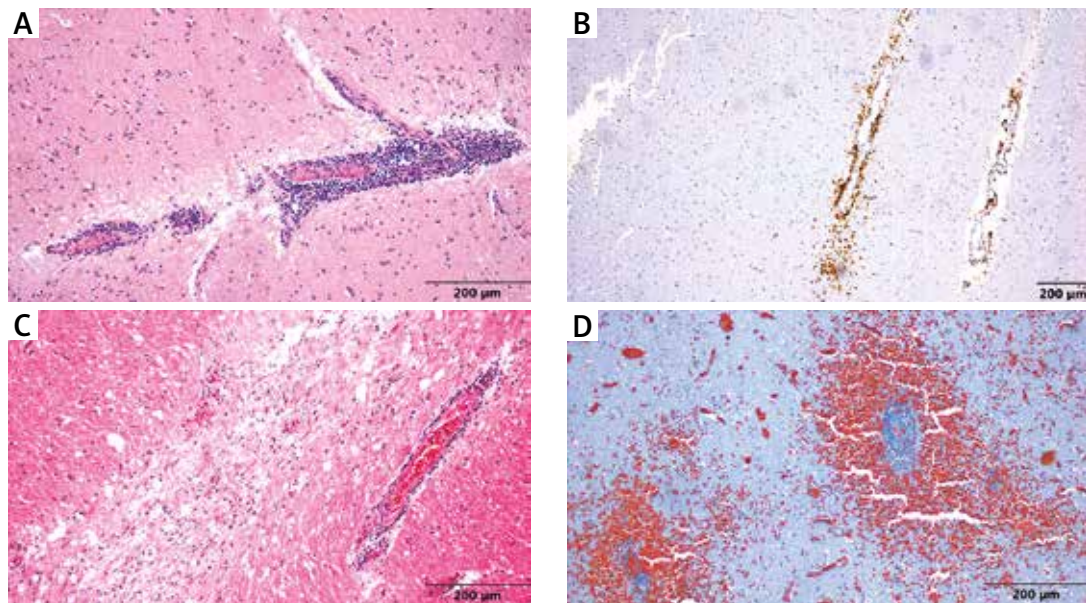


Fig. 3. Microscopic findings. **A)** HE staining of the left frontal lobe reveals severe, perivascular mononuclear inflammatory cell infiltration. **B)** CD45RO immunohistochemistry of the pons shows perivascular infiltration composed of lymphocyte T. **C)** HE staining of the pons reveals a focus of ischaemic infarct with the adjacent vessel surrounded by mononuclear cells and astroglial proliferation. **D)** Mallory's trichrome staining of the left occipital lobe discloses extravasation of red blood cells around the fibrotic vessel.

Discussion

This reported case presented several unique and interesting diagnostic challenges. Lack of autoantibodies against neuronal intracellular antigens, lack of tumour in the general autopsy and whole-body CT scan, no improvement after GKS and IVIg weaken the association with paraneoplastic aetiology. Mild CSF pleocytosis, negative blood and CSF cultures, negative PCR results, and no clinical improvement after treatment with antibiotics and anti-viral drugs indicate against viral or bacterial infection. The persistence and progression of neurological symptoms despite the correction of initial electrolyte disturbances provide evidence against CNS damage due to osmotic demyelination syndrome. Numerous other diseases with a similar clinical course were excluded as part of extensive diagnostics, i.e. Lyme disease, neurosyphilis, antiphospholipid syndrome, and CNS lymphoma. Furthermore, progressive, disseminated neurological symptoms together with multifocal, heterochronous lesions in brain MRI could suggest a diagnosis of ischaemic stroke in the course of rheumatoid vasculitis. Cerebral vasculitis is a rare complication of longstanding, seropositive RA, which may occur as a part of a systemic manifes-

tation of vasculitis or less frequently as an isolated involvement of the brain, and is usually asymptomatic with occasional cause of severe, life-threatening progressive and/or diffuse strokes [1,3,4,8,9].

Though, comprehensive radiological and laboratory evaluation were performed, the final diagnosis of encephalomyelitis due to RA was set up on the basis of post-mortem neuropathological examination. We observed numerous, disseminated, heterochronous ischaemic lesions predominantly in the brainstem and widespread, diffuse microglia, and T-cell infiltrations with neuronal loss and astrogliosis, most severe in the frontal and temporal lobes. Mild, perivascular lymphocyte T infiltrations involved particularly small and medium-sized vessels and was associated with brainstem ischaemic lesions. No neoplastic or lymphocyte B infiltration was observed. Thus, our findings correspond to other neuropathological descriptions of different kinds of encephalitis. For example, neuronal loss, gliosis, microglial cell activation, and the presence of perivascular and parenchymal infiltrating leukocytes, were reported as neuropathological features of both autoimmune and viral encephalitis [2,13,14]. Interestingly, according to the literature, Behçet disease

seems to be the most common autoimmune aetiology of encephalitis involving the brainstem [6].

To the best of our knowledge, there is only one clinical description of encephalitis associated with RA in the literature. In the publication of Kitamura *et al.* [7] a 57-year-old, previously healthy patient had headache, depression, tremor of the hands, and anorexia persisting for 7 months and mild short-term memory loss, postural hand tremors, rigidity in the upper extremities, hyperreflexia, and truncal ataxia in the neurological examination. Laboratory and radiological evaluation revealed elevated CRP, ESR, ANA, RF, CCP, mild mononuclear pleocytosis, mildly elevated protein level in CSF, and symmetric, parenchymal lesions involving the medial temporal lobes in MRI. When joint pain and swelling appeared, the diagnosis of RA was set up, and treatment with methylprednisolone, prednisolone, and methotrexate was administered with neurological and radiological improvement. In conclusion, the authors suggested AE as the first extra-articular manifestation of preclinical-stage RA. In contrast to the case presented by Kitamura *et al.* [7], our patient was older (68 years old), had a history of long-standing, seropositive RA controlled by chronic GKS, uterine cancer, and recurrent severe electrolyte disturbances; brain MRI and neurological examination indicated progressive, disseminated brain and spinal cord damage, particularly affecting brainstem, and there was no improvement after GKS treatment. Both patients had negative autoantibodies to paraneoplastic anti-neuronal and neuronal cell surface antigens. Although Kitamura *et al.* [7] suggest autoimmune aetiology of encephalitis, the aetiology in our case is more complex and includes consequences of CNS damage due to autoimmune parenchymal inflammation together with ischaemic consequences of vasculitis, ventilatory insufficiency, or hypotension. Moreover, elevated serum CCP may reflect disease activity as described Kitamura *et al.* [7], the normal levels of serum CCP in our patient may suggest previous CNS sensitization for the development of encephalitis. In summary, it seems that encephalitis/encephalomyelitis with both limbic and brainstem predominance can be an extra-articular manifestation of both preclinical or advanced stages of RA. Further research is needed to find out the pathophysiological relations between RA and encephalitis/encephalomyelitis.

In conclusion, we present the first description of neuropathological changes in a patient with encephalomyelitis associated with RA in the literature.

Our challenging clinical case underlines that both post-mortem brain examination and brain biopsy may be crucial in establishing the correct diagnosis and undertaking appropriate treatment in unclear cases with features of encephalitis and vasculitis. Thus, encephalomyelitis due to RA remains a controversial entity that needs further research and the establishment of effective diagnostic and treatment guidelines. Clinicians should be aware of encephalomyelitis as a possible CNS manifestation of RA.

Acknowledgments

This work was supported by “Digital Brain – digital collection of the Institute Psychiatry and Neurology” (Project No. POPC.02.03.01-00.0042/18-00). The project “Digital Brain” is co-funded by the European Union and the Polish budget. The authors are grateful to the First Polish Brain Bank in the Institute Psychiatry and Neurology, Warsaw, Poland.



Disclosure

The authors report no conflict of interest.

References

1. Akrouf R, Bendjemaa S, Fourati H, Ezzeddine M, Hachicha I, Mhiri C, Baklouti S. Cerebral rheumatoid vasculitis: a case report. *J Med Case Rep* 2012; 6: 302.
2. Bauer J, Bien CG. Neuropathology of autoimmune encephalitis. *Handb Clin Neurol* 2016; 133: 107-120.
3. DeQuattro K, Imboden JB. Neurologic manifestations of rheumatoid arthritis. *Rheum Dis Clin North Am* 2017; 43: 561-571.
4. Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. *Semin Arthritis Rheum* 2006; 36: 88-98.
5. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandering K-P, Waters P, Dalmau J. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; 15: 391-404.
6. Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis/brainstem encephalitis. *Curr Neurol Neurosci Rep* 2011; 11: 543-552.
7. Kitamura E, Kondo Y, Kanazawa N, Akutsu T, Nishiyama K, Iizuka T. Autoimmune encephalitis as an extra-articular manifestation of rheumatoid arthritis. *Intern Med* 2019; 58: 1007-1009.
8. Kurne A, Karabudak R, Karadag O, Yalcin-Cakmakli G, Karli-Oguz K, Yavuz K, Calgüneri M, Topcuoglu AM. An unusual central nervous system involvement in rheumatoid arthritis: combina-

- tion of pachymeningitis and cerebral vasculitis. *Rheumatol Int* 2009; 29: 1349-1353.
9. Ozkul A, Yilmaz A, Akyol A, Kiylioglu N. Cerebral vasculitis as a major manifestation of rheumatoid arthritis. *Acta Clin Belg* 2015; 70: 359-363.
 10. Prete M, Racanelli V, Digiglio L, Vacca A, Dammacco F, Perosa F. Extra-articular manifestations of rheumatoid arthritis: an update. *Autoimmun Rev* 2011; 11: 123-131.
 11. Ramos-Remus C, Duran-Barragan S, Castillo-Ortiz JD. Beyond the joints: neurological involvement in rheumatoid arthritis. *Clin Rheumatol* 2012; 31: 1-12.
 12. Sofat N, Malik O, Higgins CS. Neurological involvement in patients with rheumatic disease. *QJM* 2006; 99: 69-79.
 13. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PGE. Viral encephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol* 2005; 12: 331-343.
 14. Wierzba-Bobrowicz T, Lewandowska E, Felczak P, Stępień T, Acewicz A, Tarka S, Błażejewska-Hyżorek B, Bednarska A, Matyja E, Grajkowska W. Morphological and ultrastructural changes in Herpes simplex encephalomyelitis: an attempt to determinate the etiological factor. *Folia Neuropathol* 2020; 58: 143-150.