Changes in the natural and social environment brought about by climate change have created good conditions for the extension of the tick’s spatial and temporal distribution (14, 40). In Europe, Ixodes ricinus is the main vector of *Anaplasma phagocytophilum* (1, 25, 40, 44). *A. phagocytophilum* is a gram-negative, pleomorphic, intercellular bacteria forming macrocolonies (morulae) in infected granulocytes. It is a causative agent of equine granulocytic anaplasmosis (EGA). The severity of an EGA infection is influenced by several factors, including the strain of *A. phagocytophilum*, possible co-infections, patient age, immunological status of the infected animal, and factors such as climate and management (10, 39). The incubation period of EGA is approximately 10 days. The course of equine granulocytic anaplasmosis may be sub-clinical or acute (7, 8, 10, 29). Pyrexia, anorexia, limb oedema, icterus, petechiae, reluctance to move, and ataxia are typical clinical signs of EGA, whereas rare symptoms include recumbency (29) or rhabdomyolysis (18), cavitary effusion (33), and presumptive tick paralysis (22). Additionally, in experimentally infected horses transient systolic heart murmur has been reported (11).

*A. phagocytophilum* appears to be a rare agent in CNS infections (5, 45), which has nonetheless been observed in medical reports (16, 19, 31, 44). Severe neurologi-
cal symptoms in EGA have been previously reported (37) but never in Poland. Neurological disorders in the course of infection are also uncommon in humans (19, 20, 27, 34), sheep, cattle (39), dogs (7) and cats (1, 5, 36, 39, 41).

In human medicine, meningoencephalitis has been reported only in about 1% of cases, although the cause of neurologic dysfunction in granulocytic anaplasmosis is yet to be explained (11, 20, 27, 43). However, a number of differential system manifestations have been described, including brachial plexopathy, cranial nerve palsies, demyelinating polyneuropathy and bilateral fascial nerve palsy (16, 19, 23, 37). In case of humans suffering from HGA, neurological symptoms in the brainstem from cerebral infarction have been reported. Computed tomography (CT) shall be considered then, as a useful and appropriate tool to understand the cerebral lesions (16, 23, 35, 37).

The aim of this paper is to present the case of cerebral EGA in a horse as well as localization of comorbid hypodense cerebral changes with the use of CT.

**Material and methods**

The material for this study was based on the available literature on neurological complications after contracting anaplasmosis by humans and animals. Horses with neurologic symptoms: non-specific swellings, atactic gait, paralysis, stupor, nystagmus are also described (6, 15, 42). In other countries, acute cases of horses’ neurological disorders have been reported (15, 22, 42).

The study is also based on a clinical case of a 12-year-old mare with an open wound on the front limb at the metacarpal region that was admitted at the Surgery Clinic of Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland, in which a case of chronic cerebral anaplasmosis was diagnosed.

In the literature available, in case of horses the use of radiological imaging tools (CT, MRI) was not reported in respect of the above symptoms to locate changes in the cerebral area (35). In humans, after localization with the use of imaging diagnostics, a biopsy from the changed cerebral area may be performed (12, 35).

The changes can also be seen posthumously, macroscopically, which may indicate an advanced and intense chronic inflammatory process (Fig. 1); the pathomechanism, however, is unknown.

The basic test for anaplasmosis is the blood smear test which, however, gives a reliable result only in 30% of infected patients (2, 3, 8, 24), but never its chronic form involving neurological symptoms after several-months’ tick exposure. This case is an example of the rare chronic, neurological form of *Anaplasma phagocytophilum* infection in a horse. In other countries, acute cases of horses’ neurological disorders have been reported (15, 22, 42).

It is believed that after the tick bite, the bacterium infiltrates the blood and the lymphatic system, triggering a pathological inflammatory cascade that may damage internal organs (4, 27, 34). In cases of equine and human anaplasmosis, the neutrophils carrying the *A. phagocytophilum* pathogen circulate in the organism, probably to a greater extent than in the peripheral tissue (4, 9, 17). This may be of key significance relative to the causes of pathological lesions observed in the course of such infections. The neutrophils are involved in the inflammatory process. In *vitro* studies have also demonstrated that the bacterium inhibits the release of TNF-alpha, interleukin 6 and 13 (IL-6, IL-13) in the bone marrow mononuclear cells (BMMC) cell lines (13, 26, 30, 32).

In terms of the organ dysfunctions accompanying *A. phagocytophilum*, there have been reports evidencing hematological and biochemical disorders (7, 13, 41). Elevated levels of hepatic enzymes and hyperbilirubinemia, for example, may occur, both of which were observed in the described horse.

In humans suffering from HGA, the above factors may constitute evidence of immunosuppression. *A. phagocytophilum* has the ability to inhibit the patient’s defense
mechanisms while being poorly immunogenic itself, mainly due to the absence of lipopolisacharyd and peptidoglycan in its cellular wall (13, 31).

*A. phagocytophilum* may also target hematopoietic and lymphoreticular cells. The pathogen in question has unique pathogenic properties and shows tropism relative to the cells of the hematopoietic and phagocytic systems. Replication takes place in the phagocytic vacuoles. Intensified cytolytic activity has been observed, but it remains unclear whether *Anaplasma* directly damages cells. This probably implies the accumulation of inflammatory cells and a systemic initiation of proinflammatory response (26, 30). *A. phagocytophilum* infects endothelial and myeloid precursor cells (9, 20), human dermal cells and mast cells originating from the bone marrow, by attacking dermal mast cells in the location of the tick bite (13, 32). Symptoms include inflammation of the small arteries and veins associated with the subcutaneous fascia and distal limb nerves (4, 13). As mentioned above, *A. phagocytophilum* spreads throughout the organism via the blood and lymphatic vessels, which leads to bone marrow damage and pancytopenia, especially thrombocytopenia. The exact mechanisms responsible for the decreased platelets count in the course of the infection have yet to be discovered (13). It is believed that thrombocytopenia results from the destruction of thrombocytes by cells of the immune systems, their increased phagocytosis by macrophages and intensified breakdown in the spleen (30, 32, 41). In horses experimentally infected with *A. phagocytophilum* the autopsies revealed hemorrhages in the internal organs, kidney thrombosis and vessel inflammation (11). However, the literature does not report any consistent results evidencing a clear correlation in terms of pathological lesions in the heart, brain, kidney and skeletal muscle tissues in severe and chronic cases of anaplasmosis (11, 30, 32).

The course of granulocytic anaplasmosis in mammals can be subclinical or acute (11, 20). It should be noted that while characteristic changes in the blood are pathognomonic in the acute form of anaplasmosis, they tend to be considerably less pronounced in the chronic/subacute form. In the treated patient, alimentary tract disorders may have led to an increase in serum hepatic enzyme activity. Increased concentrations of urea were also observed in the serum of sick animals, likely due to dehydration (6). Many infections caused by *A. phagocytophilum* probably remain undiagnosed. Subclinical infections are common while the diversity of the symptoms, including clinical ones, is not pathognomonic (21, 24). The observed symptoms may range from mild fever to potentially life-threatening complications, a factor which hinders early diagnosis, particularly in animals. Clinical neurological symptoms that may derive from the CNS pathologies are not commonly reported in horses suffering from anaplasmosis.

CT scans may help to verify brain lesions in the context of clinical neurological symptoms (16, 23, 35, 43).
thousands of cerebral microinfarctions that considerably disturb structural cerebral connections (28). In its last month, the described mare suffered from intensified gait disorders and recumbency, which may have resulted from the coexistence of the anaplasmosis and microinfarctions (12).

In a study on middle cerebral artery occlusion in Wistar rats, in isolated infarction locations only a small number of neurons with signs of necrosis were observed in the first 4 hours. The earliest significant increase in the percentage of necrotic neurons (15%) in the region of the obstructed artery was reported only after 6 hours. The results correlate with reports concerning the progress of neuronal necrosis after permanent closure of an artery. The reasons for the progression of the lesions are unknown. It remains to be determined whether the extent of the neurological deficit caused by arterial closure correlates with the number of necrotic neurons. It has been confirmed that cerebral microinfarctions can continue for up to several weeks. A microinfarction causes functional hemodynamic deficits and neuronal defects in the surrounding tissue. Neuronal function is impaired in the cortical regions, at least 12 times larger than the size of the stem lesion itself. Patients may show functional disorders (12, 28).

Computed tomography is not the modality of choice for assessing microinfarcts. This type of lesion can be detected by using MRI, especially in T2-weighted and FLAIR sequences.

The samples for histopathology were taken from the medulla oblongata and the temporal part of the cortex. Microscopic examinations of the gray matter revealed microfoci of perivascular necrosis, signs of neuronal vacuolization, degeneration, necrosis and loss. Focal axonal necrosis and spherulosis were noted within the gray matter (Figs. 4, 5). Reactive proliferation of the microglia close to degenerative neurons was noted. There were signs of intensive spongiosis within the medulla oblongata, inadequate to the age of the animal (Fig. 6).

The determination of the actual correlation between anaplasmosis and cerebral infarction requires further research. It should also be determined whether cerebral infarctions can result from thrombosis caused by damage to endothelial cells, which may be hypothetically triggered by *A. phagocytophilum*, or as in other cases of rickettsia, by platelet diffusion (16, 22).

Given the growing incidence of tick-borne diseases, both in humans and animals (11, 38, 40, 44) living in endemic regions for anaplasmosis, in cases with coexisting neurological disorders potentially related to CNS, *A. phagocytophilum* ought to be considered as a possible cause of clinical symptoms in the course of differential diagnostics. The most pressing challenge currently relates primarily to the ability to quickly diagnose an infection caused by *A. phagocytophilum* given the nonspecificity of its clinical symptoms and the intracellular character of the pathogen (16, 23).

Computed tomography has served as a useful tool for assessing changes in the brain. Hypodense changes...
cal neurological symptoms, patients were referred for CT or MRI scans. The diagnosis of such cases, both in humans and animals, causes many difficulties (in the case of treating horses, especially those who work in the field). Perhaps the article could serve as an example to consider anaplasmosis in the differential diagnosis as a potential cause of the disease, especially in endemic areas, even several months after the animal’s exposure to ticks in the case of nonspecific, complex neurological symptoms. The article may also draw attention to the need to examine the CNS area in the case of confirmed anaplasmosis in order to explore the pathomechanism of changes visible in the radiological image. This highlights the importance of imaging to explain the nature of the observed neurological deficits in animals.

References


Corresponding author: Izabela Polkowska, Department and Clinic of Animal Surgery University of Life Sciences in Lublin, ul. Głęboka 30, 20-612 Lublin, Poland; iza-polkowska@tlen.pl