Case Report

Zoonotic Infection with Rabies Virus Leading to Fatal Encephalitis in Pediatric Patient – Case Report

Gheorghita Jugulete [1,2,#], Madalina-Maria Merisescu [1,2,*#], Alexandra Bastian [1,3,#] , Sabina Andrada Zurac [1,3,#], Carmen Pavelescu[1,#] and Monica Luminita Luminos[1,2,#]

[1] Faculty of Medicine, University of Medicine and Pharmacy, "Carol Davila", No. 37, Dionisie Lupu Street, 2nd District, 020021 Bucharest, Romania
[2] "Matei Balş" National Institute for Infectious Diseases, No. 1, Calistrat Grozovici Street, 2nd District, 021105 Bucharest, Romania
[3] Colentina Clinical Hospital, 020125 Bucharest, Romania; Department of Pathology.
* Correspondence: Mădălina Maria Merișescu , madalinamerisescu@gmail.com;
#All authors contributed equally to this work.
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Abstract: Rabies is a life-threatening and vaccine-preventable infectious disease triggered by an RNA virus, part of the *Rhabdoviridae* family, *Lyssavirus* genus. It is transmitted from infected saliva, blood, or organs from rabid animals to humans. Children are at high risk due to their inability to defend themselves from infected animals and most deaths occur in this age category (under 15 years). Rapid diagnosis and humans postexposure prophylaxis (PEP) is standard and lifesaving at the same time with early elimination of rabid animals. In this case report, we describe a rabies case in a ten-year-old female child, bitten by a cat ten days before hospitalization. Despite the challenges to obtain a rabies laboratory diagnosis, and the maximal treatment introduced from early admission (Human Rabies Immunoglobulin, anti-rabies vaccination, orotracheal intubation and mechanical ventilation) the evolution of the patient was unfavorable, namely death one months after admission. The objective is to understand the mechanism of infection and mortality from rabies virus in children with neurological symptoms and without PEP. The rate of human exposure may be significantly decreased by controlling rabies through pet immunization programs and presentation to the hospital as soon as an aggression from animals occurred.

Keywords: rabies; children; postexposure prophylaxis; zoonotic disease; vaccine; wound treatment

1. Introduction

Rabies is a zoonotic disease determined by a single-stranded RNA virus, which belongs to the *Lyssavirus* genus, Order *Mononegavirales*, *Rhabdoviridae* family, that kills every year approximately 59000 people worldwide [1-4]. PEP is necessary to be started as early as possible and this estimates to prevent hundreds of thousands of rabies deaths annually [5]. Wound cleansing management and simultaneous administration of rabies immunoglobulin (RIG) combined with anti-rabies vaccine (ARV) is almost invariably effective even after high-risk exposure and should be started as early as possible after a contaminated event [6]. Fatal failures of PEP, when occurs, are typically associated with insufficient or delayed PEP treatment. Nevertheless, insufficient therapy may result in delayed or suboptimal RIG administration, as well as inadequate injection of wounds which is constrained in pediatric patients by low body weight. If the body-weight-based RIG dose's volume turns out to be insufficient, volume expansion through dilution will be required to achieve complete virus neutralization and adequate infiltration into all wounds [7,8].

In Romania, a scarce number of rabies cases are reported in both animals and humans. In children, rabies cases are extremely rare, the infection being produced through contaminated domestic animals [9-11]. The rabies virus is transmitted from sick animals when infected saliva contact with open wounds such as those caused by bites or scratches,

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and when it meets the surfaces of the human mucosa [1,4,12]. The rabies virus usually penetrates the body through the wound produced by the bite of an infected animal (its saliva containing the virus) and by way of fillets, reaches the brain, triggering characteristic lesions. Literature accounted for some cases of rabies transmitted through aerosols or mucous membranes (accidentally in laboratories). [13-15]. The more the area where the bite is located is innervated (fingers, genital area) or closer to the brain (face) the shorter the time of incubation. From the clinical standpoint, there are two forms of rabies: furious and paralytic, both preceded by a prodrome with a characteristic clinical picture. The most frequently described cases are furious clinical forms with more rapid evolution towards death [16]. The rabies virus can be isolated by in situ hybridization methods (RT-PCR-polymerase chain reaction) that can identify the virus at the level of the wound, the saliva, or the central nervous system. Postmodern diagnosis of rabies is established by anatomopathological examination which highlights, by immunohistochemistry techniques, the presence of Babes-Negri bodies, pathognomonic for rabies. Electronic microscopy can also evince the rabies virus in the hippocampus as well as in other tissues. Rabies treatment is only prophylactic (immunoglobulins and vaccination), with other methods (prolonged sedation, decrease in the body temperature) having had recorded meaningful results, so far. Once obvious clinical signs have occurred rabies evolves severely, leading to death [17-20].

2. Case report

We aim to present the case of a ten-year-old female patient, admitted with rabies in the Paediatric Intensive Care Unit at National Institute for Infectious Diseases „Prof. Dr Matei Bals", Bucharest. Anamnesis revealed that the patient had been bitten by a cat (category III -Lyssavirus exposure), ten days before hospital admission, the bite inflicting a wound at the level of the hand. The cat was known to the family, didn't receive anti-rabies vaccination, and had aggressive behavior which raised the suspicion of animal rabies.

Upon admission, the patient presented a critically altered general state, with severe psychomotor agitation that alternated with rare periods of consciousness, visual and auditory hallucinations, significant hypersomnia, aerophobia and hydrophobia, tachycardia (VA- 170b/min), polypnea (40-50/min), SpO2 - 95% in atmospheric air without signs of meningeal irritation. The onset of symptomology was 24 hours before hospitalization.

Biological samples taken at the time of admission did not record significant changes, except for increased LDH (Lactate dehydrogenase) and muscle enzymes (CK) and discreet hepatic cytolysis as well as persistent elevated BUN (blood urea nitrogen) and creatinine levels. IgM serology for viral illnesses was negative, except for this etiology. We also appealed to differential diagnosis, outlining all the diseases with a similar clinical picture (acute meningoencephalitis, acute encephalopathy, coma of various causes, acute intoxication). The RT-PCR confirm the presence of rabies virus skin, hair follicles, cerebrospinal fluid (CSF) based on RT-PCR (diagnostic method subsequently licensed- GenBank BankIt Submission ID: 1976388). Necropsy samples were taken from the brain and found Babes -Negri bodies in the hippocampus. See microscopic images attached (Fig.1-Fig.10).

Based on the clinical signs, epidemiological data, and the identification of the rabies virus in CSF the diagnosis of rabies encephalitis-furious form was established. Specific rabies immunoglobulin therapy, of equine origin, was initiated, with sensitivity testing and progressive desensitization, followed by anti-rabies vaccination (therapeutic scheme applied on days: 0, 3, 7, 14, 28) without any records of allergic incidents. Furthermore, until the rabies diagnostic was confirmed, we also introduced acyclovir treatment. Therapy was supplemented with anti-oedema drugs (Mannitol and Furosemide), anti-inflammatory steroids (Dexamethasone), unspecified human immunoglobulin, acid-base and hydro electrolytic rebalancing, and symptomatic drugs.

Evolution was rapidly unfavorable, with the onset of an acute cardio-respiratory failure that required the induction of coma and orotracheal intubation with mechanical ventilation, in less than 24 hours from admission. Also, to preserve the brain functions we

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induced hypothermia by decreasing the body temperature to 34ºC, however without any positive outcomes. Despite the complex treatment, evolution was unfavorable with the onset of Multiple Organ Dysfunction Syndrome (MODS) (kidney, liver, hematologic, neurologic) and mechanical ventilation-associated bronchopneumonia, the patient's death occurring 30 days after admission.

Subsequently, the anatomopathological examination confirmed the established diagnosis, highlighting (figure 1 – 10).

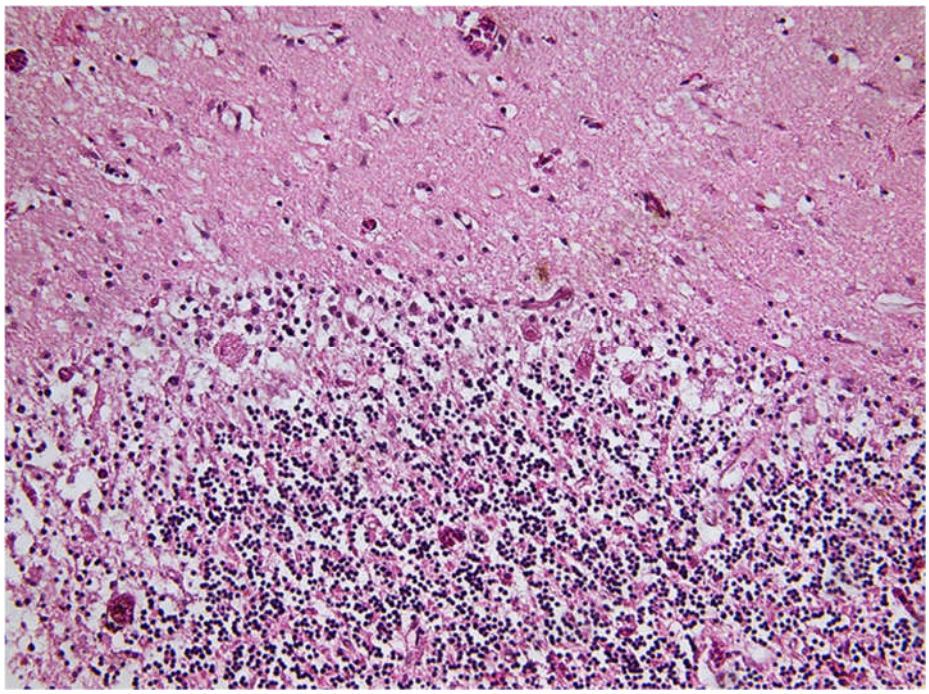

Figure 1. - Babes-Negri intracytoplasmic round eosinophilic, sharply outlined inclusions in the Purkinje cells of the cerebellum containing the rabies virus (Hematoxylin and eosin stain; magnification x 200).

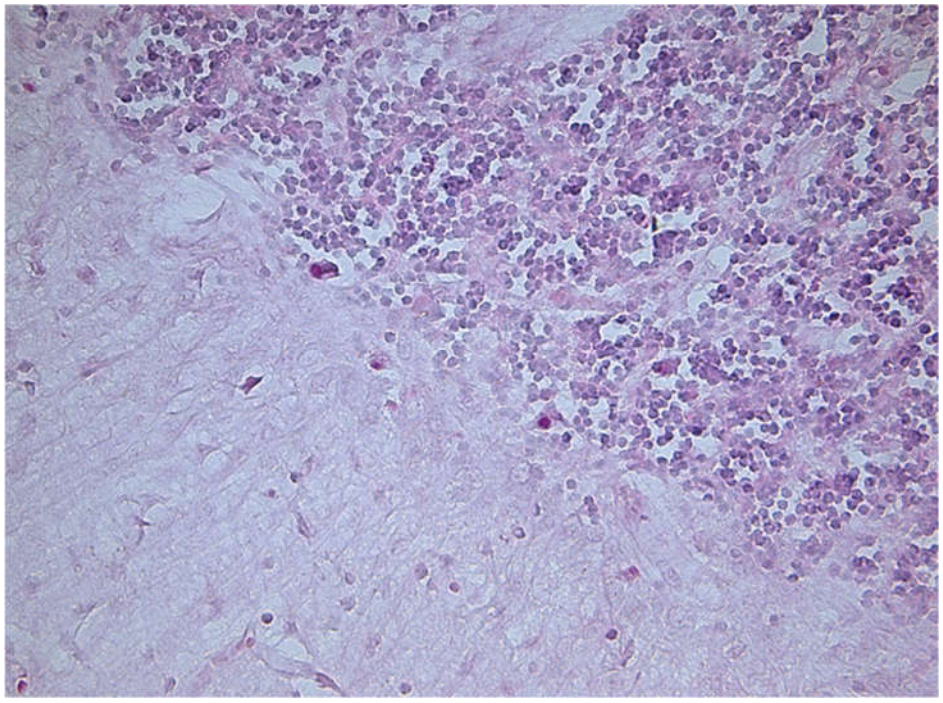

Figure 2. - Purkinje cells of the cerebellum with Babes-Negri intracellular inclusions magenta colored with Mann staining (magnification x 400).

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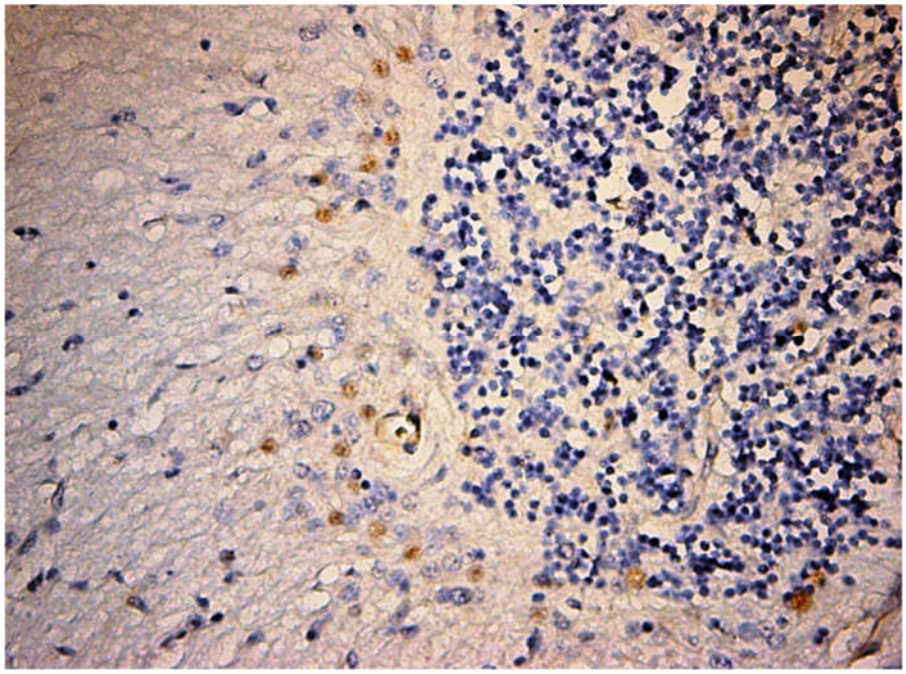

Figure 3. - Immunohistochemistry using anti-rabies virus antibody highlighting the rabies virus antigen in the perikaryon of the cerebellar neuronal cells (magnification x 400).

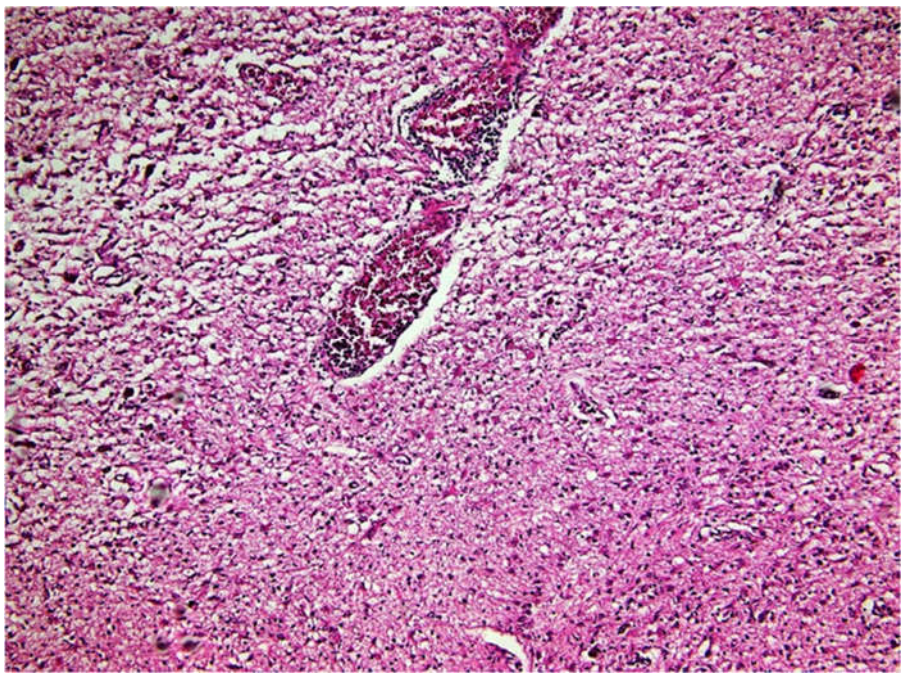

Figure 4. - Mononuclear infiltration in the hippocampus (Hematoxylin and eosin stain; magnification x 200).

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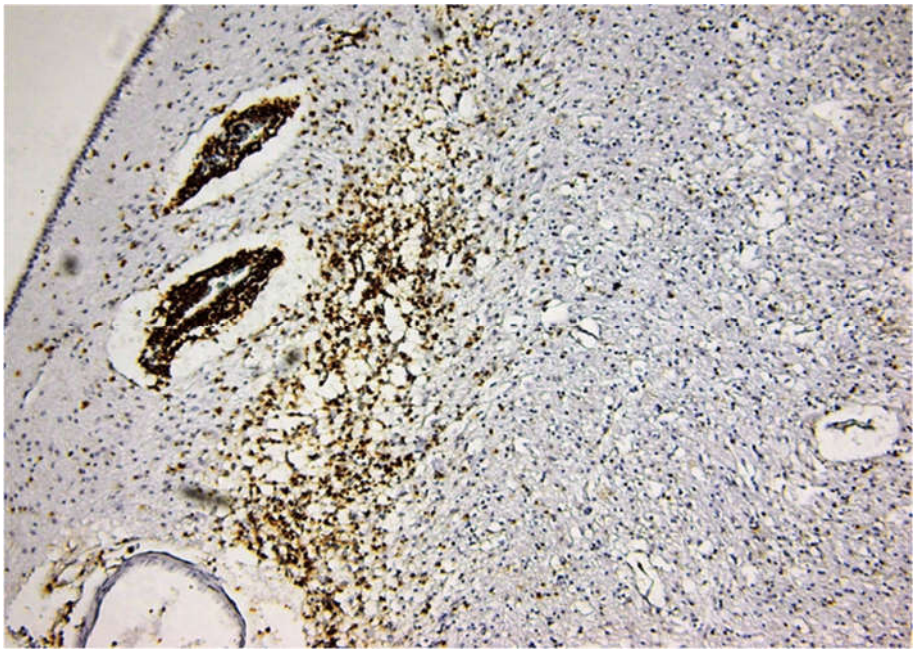

Figure 5. - Subependymal and intracortical encephalitis with diffuse and perivascular cuffing of mononuclear inflammatory cells revealed using immunohistochemistry for Leukocyte Common Antigen (LCA-antibody, magnification x 100).

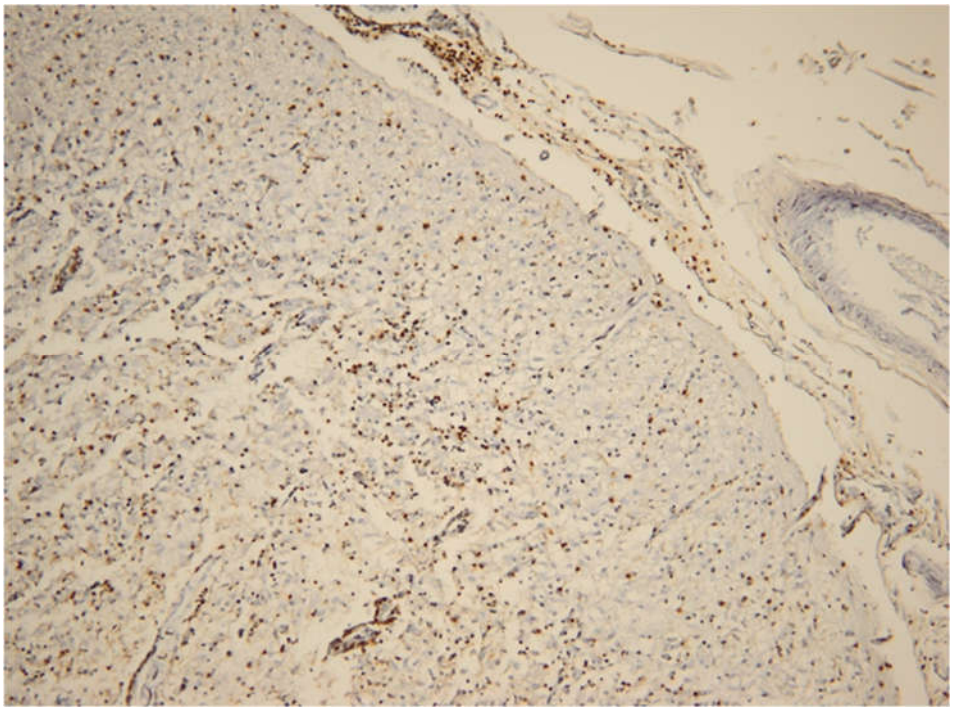

Figure 6. - Subependymal and intracortical encephalitis with diffuse and perivascular cuffing of mononuclear inflammatory cells revealed using immunohistochemistry for Leukocyte Common Antigen (LCA-antibody, magnification x 100).

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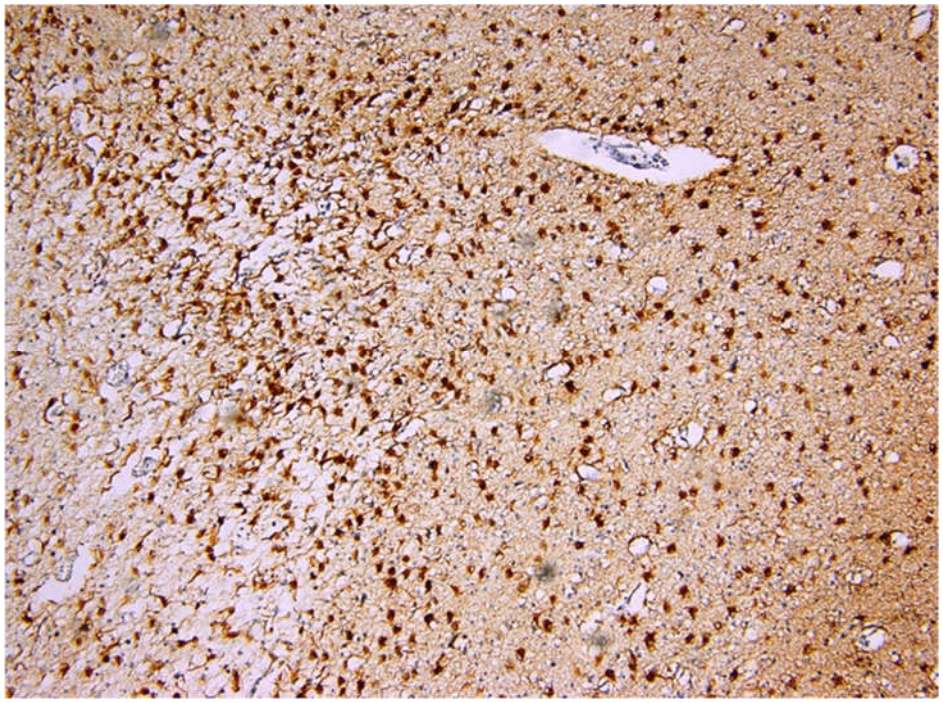

Figure 7. - Evenly dispersed reactive astrocytes with long, star-like cytoplasmic processes in the hippocampus, demonstrated utilizing immunohistochemistry for glial fibrillary acidic protein (GFAP, magnification x 100 and x 200).

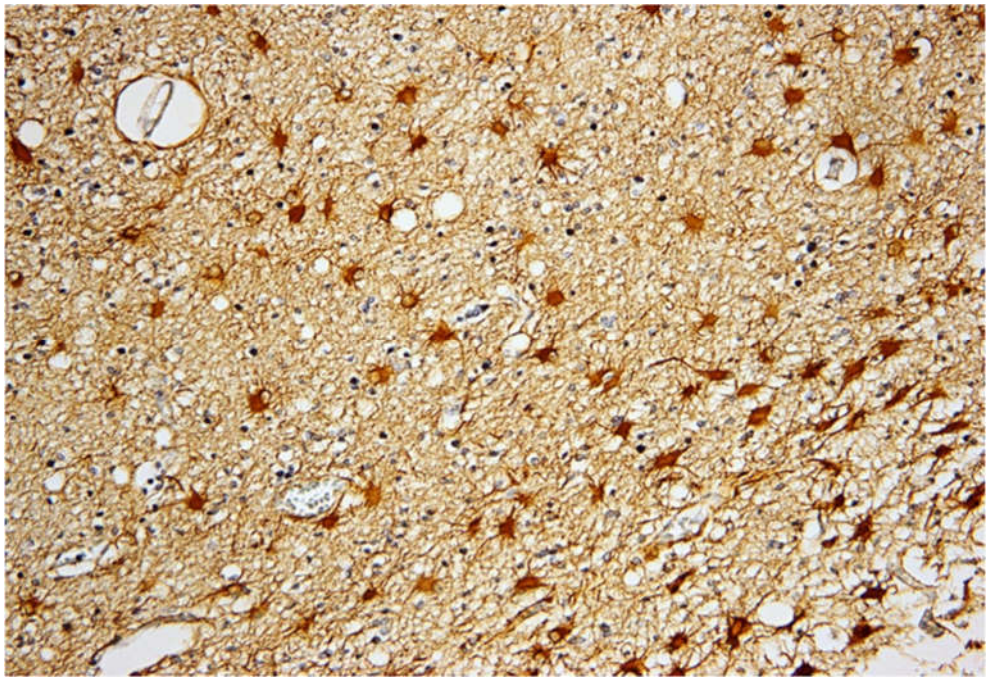

Figure 8. - Evenly dispersed reactive astrocytes with long, star-like cytoplasmic processes in the hippocampus, demonstrated through immunohistochemistry for glial fibrillary acidic protein (GFAP, magnification x 100 and x 200).

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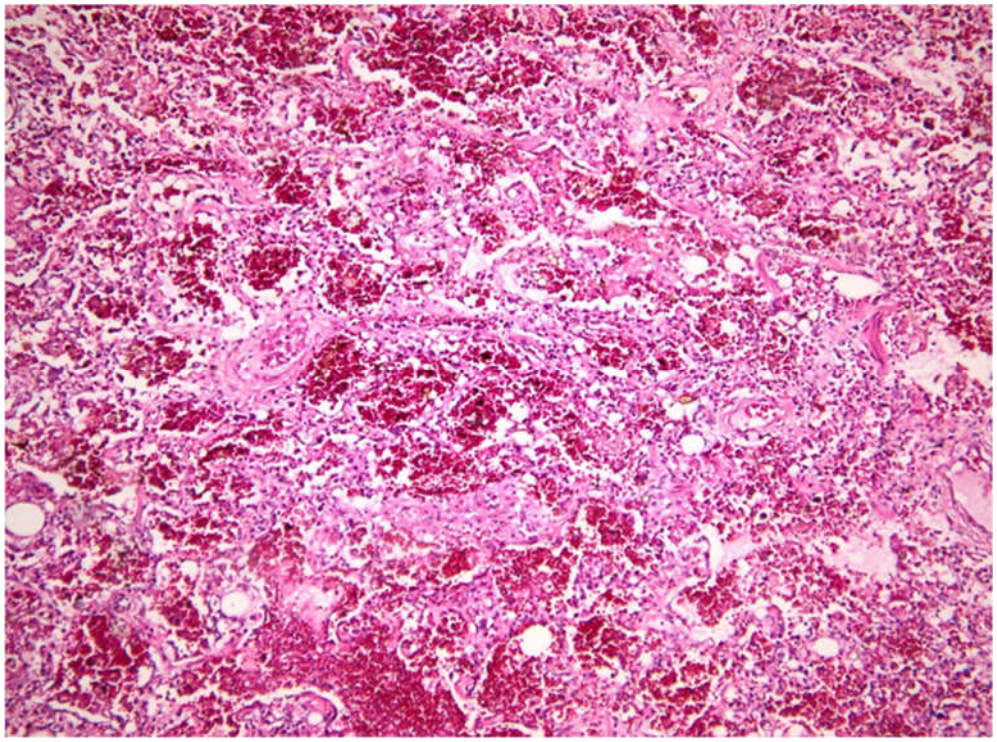

Figure 9. - Lung with edematous alveolitis, diffuse intra-alveolar hemorrhage and some alveolar walls lined by hyaline fibrinous membranes (Hematoxylin and eosin stain; magnification x 100).

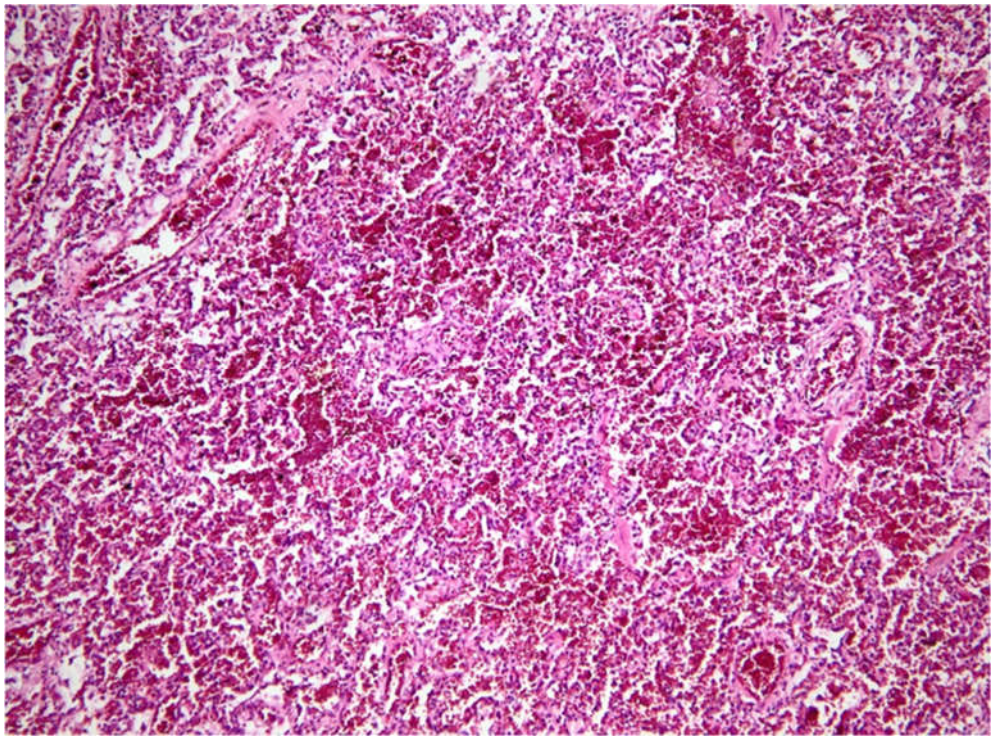

Figure 10. - Lung with edematous alveolitis, diffuse intra-alveolar hemorrhage and some alveolar walls lined by hyaline fibrinous membranes (Hematoxylin and eosin stain; magnification x 100).

3. Discussions

Through the present material, we outlined a case of pediatric rabies, the clinical furious form, having as the source of infection a domestic animal (rabid cat - without diagnostic confirmation) who, initially, didn't receive specific prophylaxis (only 10 days after the infecting bite, in our clinic). Early administration (within the first hours from the

infectious bite) of passive prophylaxis (anti-rabies immunoglobulin) followed by anti-rabies vaccination would have led to a better outcome in terms of evolution and prognostic. From the standpoint of positive diagnostic, this was established based on clinical and epidemiological data, with histopathology confirmation (postmortem). Likewise, the diagnostic was confirmed antemortem by identifying the rabies virus in CSF by PCR. In our clinic we have also used this method of diagnosis in a child with rabies, a case presented and published in the journal „Rabies Bulletin Europe" [21]. This method is useful because it helps clinicians establish an early diagnosis of rabies, with the introduction of specific treatment which ultimately would trigger a better prognostic for this affection. Evolution was unfavorable, despite the complex treatment (anti-rabies, pathogenic, symptomatic drugs, induced coma with intubation and mechanical ventilation, hypothermia), the patient dying due to Multiple Organ Dysfunction Syndrome (MODS) and complications associated with prolonged mechanical ventilation (30 days).

5. Conclusions

Rabies is an extremely severe disease that causes death in all cases once the characteristic clinical picture is installed (the presence of rabies virus in CNS). Despite the availability of passive and active prophylactic measures, there are a few, isolated cases of human rabies because of infection by contact with rabid animals. By applying all standard prophylactic measures as early as possible (within the first hours from the possible infectious contact), the number of human rabies would decrease significantly. Also, the elimination of animal rabies outbreaks in our country would contribute to the eradication of a severely, lethal illness. Rapid establishment of a positive diagnostic, before the onset of the specific clinical picture of encephalomyelitis by confirmation with modern techniques (PCR from CSF or at the level of the wound), would decrease the rate of death by rabies due to early initiation of a specific therapy.

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Institutional Review Board Statement: Written informed consent was obtained for the study of the rabies virus in the patient's autopsy samples.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement The data that support the findings of this study are available on request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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