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Case Report: Encephalopathy after Ivermectin Treatment in a Patient Infected with *Loa Loa* and *Plasmodium* spp.

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Abstract. Despite over 350 million people being safely treated with ivermectin, there have been rare cases of death post-treatment; these events are most often associated with high *Loa loa* microfilaremia. This first autopsy description of an encephalopathy case following the administration of ivermectin involves a 45-year-old male who became comatose 3 days after treatment. He slowly deteriorated over 5 weeks and died at 54 days after the anthelminthic treatment, probably as a result of a secondary skin or pulmonary infection exacerbated by malnutrition. The major pre- and post-autopsy findings included the presence of high loads of *Loa loa*, positivity for *Plasmodium*, the presence of a longstanding respiratory condition, and vascular pathology in the brain. The central nervous system lesions have similarities with those described in previously reported cases of *Loa loa*-associated death following diethylcarbamazine treatment.

INTRODUCTION

Onchocerciasis control is currently based on mass community-directed treatment with ivermectin. In Africa, the drug is usually distributed annually, and in 2006 some 50 million treatments were provided through the Mectizan Donation Program to the African Program for Onchocerciasis Control (APOC). Since the early 1990s, cases of neurologic serious adverse events (SAE) have been reported from Central Africa.[1] Studies conducted in Cameroon demonstrated that these problems occur in patients harboring *Loa loa* microfilaremias exceeding 30,000 microfilariae (mf) per mL of blood.[2,3] Though rare, these SAEs necessitate the implementation of a strict surveillance system, and are thus an impediment to the implementation of APOC activities in the areas where the prevalence of *L. loa* filariasis is high and there is a risk of their occurrence.[4]

The mechanisms associated with the neurologic SAEs are poorly understood,[5] making it difficult to recommend a treatment or perform any other activities that might improve or prevent the condition. Fundus examinations of patients have shown that these post-ivermectin neurologic SAEs are often associated with retinal hemorrhages and exudates evocative of an obstructive process.[6] Similar processes might occur in the brain, but to date no central nervous tissue has been collected from patients suffering a fatal outcome. This present communication describes the clinical course and the tissue pathology in the first case of post-ivermectin *Loa* encephalopathy where an autopsy has been performed.

CASE REPORT

The patient was a 45-year-old male living in the village of Foabang, which is located in the Mayo Banyo Division (south-west of the Adamaoua Province of Cameroon) and in the Songkolong health area (which is part of the Bankim health district). The area corresponds to the northern part of the Tikar plain, which is covered by a shrub savanna crossed by forest galleries, and where endemicity for loiasis is high.[7,8]

The patient had a longstanding history of cough, but his family reported that he did not show any other abnormal signs or symptoms before treatment and had none of the usual clinical manifestations of malaria (he was subsequently found to be infected with *Plasmodium* spp.). He received ivermectin (Mectizan®) treatment for the first time with the standard dose (150 μg/kg) on June 1, 2003 (Day 0) as part of the community-directed treatment with ivermectin (CDTI) organized in the Adamaoua province. In the evening of the same day, he complained of joint pain, dizziness, and was feverish. During the night, he was unable to stand up without help. On Day 3 the patient began to speak incoherently, and by the next day did not speak any more and was taken to the Songkolong Health Center. On admission to the Health Center, the patient was asthenic, dyspneic, and his body temperature was 38.5°C. A blood smear showed the presence of many *Loa loa* mf and *Plasmodium* spp. parasites (recorded semi-quantitatively as ++ out of a maximum of +++). By the evening, the patient was comatose and his body temperature 39.8°C; an intra-venous quinine infusion was started. In the morning of Day 5, his clinical condition had not changed significantly, and he was transferred to the Bankim District Hospital. On admission, the comatose patient reacted only to pain stimuli of medium intensity, his breathing was ample and noisy, his temperature 39.0°C, and he presented with hemorrhages of the palpebral conjunctiva. An infusion of Ringer's lactate, glucose, KCl, and calcium gluconate was administered, and a regimen of 600 mg quinine twice a day for 7 days was initiated. In the afternoon of Day 5, the patient suffered an episode of partial seizure of the head, associated with slobbering and chattering of teeth; he was given a 10 mg phial of diazepam. A thick blood smear prepared on Day 5 revealed a *Loa* microfilaremia count of 1,300 mf/mL. In the evening, the temperature was 37.2°C. Between Day 6 and Day 9, his body temperature fluctuated between 36.5 and 39.6°C. Examina-

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tion of the blood on Day 6 revealed a leukocyte count of 3,900/mm^3 (neutrophils: 72%; eosinophils: 6%; lymphocytes: 22%). A sample of cerebrospinal fluid (CSF) obtained by lumbar puncture the same day was crystal clear but contained many mf, the species of which was not determined; a Gram stain of the CSF was negative for bacteria. Urine examination showed the presence of leukocytes (1–2 per field of a centrifuged sample) and *Loa* mf. The patient was then fed through a naso-gastric tube. A treatment schedule of 1 g chloramphenicol every 6 hours for 9 days and 1 g piracetam three times a day for 2 weeks was added to the infusion and quinine treatment. Although a strict nursing regimen was put in place, the patient developed bedsores, most likely due to the type of bed and mattress available at the hospital.

On Day 9 his temperature was 37.0°C, his Glasgow coma score 5/15, and he showed signs of dehydration (decreased skin turgor), hemorrhages of the palpebral conjunctivae, and multiple bedsores. Auscultation showed muffled heart sounds, and crackling in both lungs. The tendon, corneal, and pupillary reflexes were present and normal. The laboratory tests performed at this time showed the following: sodium concentration: 138 mmol/L (normal: 135–145 mmol/L); potassium: 5.3 mmol/L (normal: 3.5–5.0); chlorides: 88 mmol/L (normal: 100–108); calcium: 74 mg/L (normal: 85–105); phosphate: 61 mg/L (normal: 25–50); magnesium: 0.7 mmol/L (normal: 0.7–1.0); proteins: 62 g/L (normal: 60–80); creatinine: 14 mg/L (normal: 6–15); ASAT/SGOT: 45 U/L (normal: < 25); ALAT/SGPT: 38 U/L (normal: < 55); C-reactive protein: 123 mg/L (normal: < 6 mg/L); hemoglobin: 130 g/L; red blood cells: 4.19 10^{12}/L; white blood cells: 8.1 10^9/L; eosinophils: 1.79 10^9/L; hemoglobin electrophoresis: hemoglobin AA. The *Loa* microfilarial load at that time was 3,600 mf/mL.

The patient's condition remained more or less stable up to Day 31 and he continued to receive rehydration infusions and was tube-fed throughout this period. His temperature usually remained below 39.0°C with rare peaks of 39.0°C. By Day 31 his state of consciousness had improved and he was able to respond to verbal stimulations. On Day 38 the patient was no longer comatose and could speak, though with difficulty, and could swallow liquid food; his Glasgow score was 13/15. However, the patient was emaciated, still incontinent, and had bedsores in the trochanter and the lumbar regions, as well as edema of his left leg. A blood smear performed the same day showed a *Loa* microfilaremia at 80/mL. The patient died on Day 54, and following agreement from his family, an autopsy was performed 15 hours after death. Samples of lungs, heart, spleen, liver, kidney, and the frontal lobe of the brain were fixed in a 10% formalin solution.

HISTOPATHOLOGY

Macroscopically, the lungs showed diffuse black spots similar to those seen in anthracosis; the heart was slightly enlarged in volume and the spleen showed diffuse yellowish spots. The brain was normal in gross appearance. Following paraffin embedding and sectioning the tissues were stained with a range of histochemical (hematoxylin and eosin, Giemsa, and silver stains) and immunochemical reagents (antibodies directed against Factor VIII, macrophages [Mac 1 marker], pan T cells, B cells, and against glial fibrillary acidic protein—GFAP—a marker for astrocytes) using standard immunocytochemical procedures.

No microfilaria or any other helminth parasite was found in any of the tissues examined. The lung samples showed extensive changes, with neutrophil infiltration of the alveolar walls and spaces consistent with severe acute pneumonia of clinical significance. The spleen showed a mild histiocytosis in the red pulp, but no other significant anomalies. Mild mononuclear cell infiltrates were present in most portal zones of the liver. The kidney tissues showed mild thickening of the glomerular basement membrane and minor degrees of interstitial fibrosis in certain limited areas, none of which was considered to be clinically significant.

Two major changes were seen in the brain tissue, both mainly in association with the small and medium size blood vessels. The first consisted of moderate perivascular accumulations of inflammatory cells (Figures 1A and 1B), largely consisting of lymphocytes (T cell positive) and macrophages (Mac 1 positive) with associated pigmentary (hemosiderin) deposits. Secondly, there were significant thickenings of the basement membrane and associated pericytic layer of various-sized vessels (Figures 2A and 2B); in some cases there was apparent disruption of the integrity of the vessel wall. These infiltrates were more commonly seen around the vessels that had an increased deposition of collagen; a few such isolated cellular infiltrates were also seen in the parenchyma, usually in close proximity to affected blood vessels. In addition, areas of mild reactive gliosis associated with mild demyelination were also observed. The majority of these pathologic changes were present in the deeper tissues of the cerebral cortex. There was no histologic evidence consistent with recent major thrombotic events or acute necrotizing vascular events.

DISCUSSION

To date more than 120 cases of "Probable *Loa* encephalopathy temporally related to Mectizan treatment" (PLERM), as defined by Twum-Danso and Meredith (2003), have been reported, mainly from Cameroon and Democratic Republic of Congo (DRC); most of these cases recovered without serious consequence. The uncertainty of the mechanisms associated with the PLERMs,[3,5] has been in part due to the lack of any autopsy-derived information. The present paper describes the first case where an autopsy could be performed; it was performed shortly after the patient's death, thanks to the specific surveillance system for PLERM that has been put in place in Cameroon. The definition of this case as a PLERM[9] is supported firstly by the typical changes in this individual's clinical condition within the few days after the treatment, secondly by his post-treatment level of the *Loa* microfilaremia (> 1,000 mf/mL within 1 month post treatment), and also by the presence of mf in the CSF.

Previous estimates suggested that the *Loa* microfilarial loads measured 7–15 days after a standard dose of ivermectin corresponds to 15–20% of the pre-treatment value.[3] Thus it can be surmised from Day 9 mf load of 3,600 mf/mL that this patient would have harbored an initial load of between 18,000 and 24,000 mf/mL (i.e., a relatively low value when compared with the pre-treatment levels in other patients who have developed a PLERM).[10] However, data obtained from the only three cases of *Loa* encephalopathy for whom the microfilaremias have been measured before treatment and then within the first days after treatment underscore the large differences

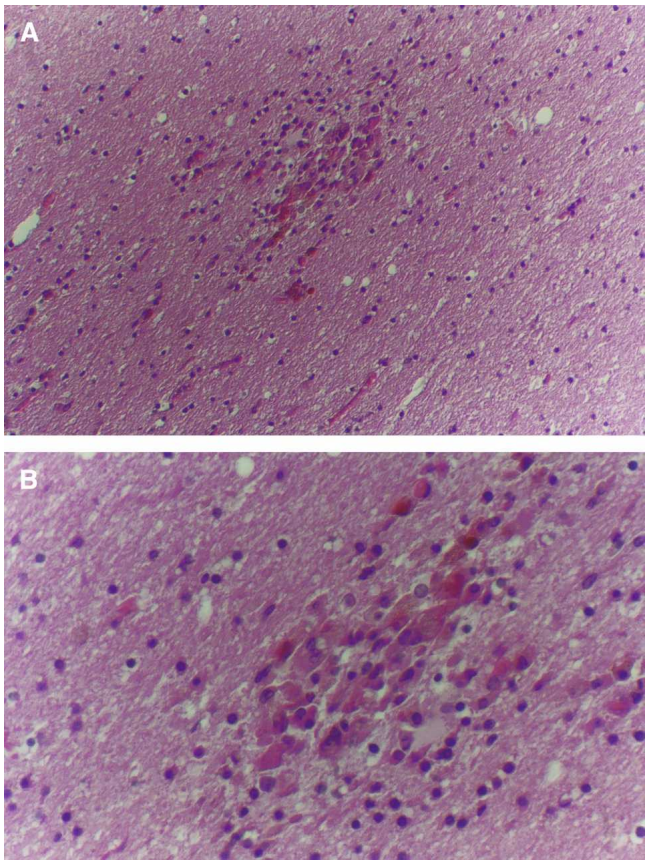

FIGURE 1. CNS of the *Loa loa* encephalopathy patient. **A**, Chronic cellular focus in brain parenchyma. **B**, Higher power of the cellular focus showing pigment present in macrophage cells.

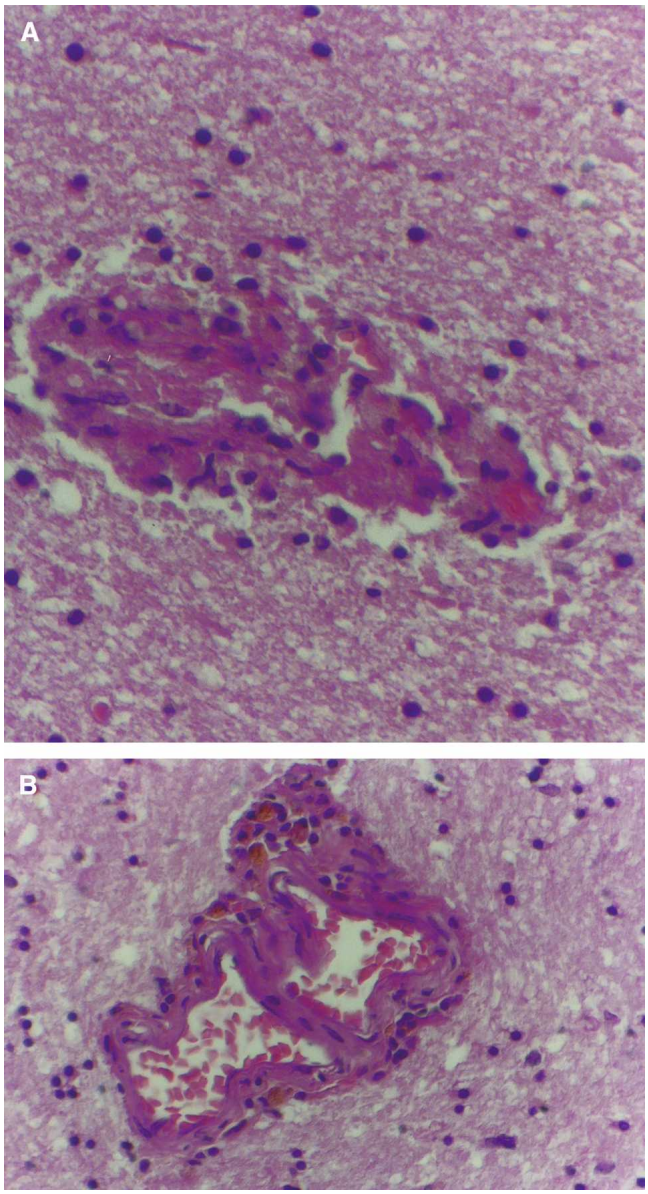

FIGURE 2. Vascular changes commonly seen in the brain of the *Loa loa* encephalopathy patient. **A**, Cellular infiltrates, thickening of the vessel wall. (**B**) The accumulation of pigmented material in phagocytes.

in blood count that occur. In one case, the values at Day 0, Day 1, Day 2, and Day 3 were 162, 920, 90,520, 7,290, and 1,880 mf/mL, respectively; in the second case, the microfilaremias on Day 0 and Day 4 were 152,940 and 17,700 mf/mL; and in a third patient, the values on Day 0 and Day 4 were 50,520 and 1,420 mf/mL, respectively.[10] It is notable that values recorded on Days 3 and 4 in two of these cases were lower than that recorded on Day 9 in the present case. Thus it is possible that the pre-treatment mf load in the present case was actually higher than the 30,000 mf/mL threshold above which a patient is at risk of developing a PLERM. These findings underline how important it is to determine the pattern of decrease in the *Loa* microfilaremia after ivermectin treatment in patients harboring high initial loads.

Although it is clear that the main risk factor associated with PLERM is a high pre-treatment level of *Loa* microfilaremia, the majority of those patients who harbor high *Loa* loads do not actually develop such a neurologic SAE after ivermectin treatment. This suggests that co-factors, including co-infections liable to weaken the blood–brain barrier (BBB), might play a crucial role in the development of the condition. This possibility has often been considered in the case of spontaneous or post-diethylcarbamazine (DEC) *Loa* encephalopathies. Various types of infections have been mentioned as possible co-factors: trypanosomiasis,[11,12] syphilis,[12] acute encephalitis,[13] infection associated with flu symptoms,[14,15] local suppuration,[13] and *Plasmodium* infection.[1,13,16,17] In relation to the latter infection, one that is common in Africa, it is interesting to note that the patient described in the present paper was positive for *Plasmodium* spp. A study was conducted in Cameroon on 4,169 individuals (Kamgno J and others, unpublished data) to evaluate whether a co-infection with *Plasmodium* increases the risk of developing a post-ivermectin *Loa*-related neurologic SAE. None of the patients developed neurologic SAE, although 18 had some form of non-neurologic functional impairment requiring hospitalization; co-infection with *Plasmodium* was not associated with the risk of developing such a non-neurologic SAE. Thus a role for *Plasmodium* infection in the pathogenesis of PLERM remains undefined. It is conceivable that high *Plasmodium* loads could bring about lesions at the level of the brain capillaries. Unfortunately, in the present case, the density of *Plasmodium* parasites was not accurately assessed before the implementation of the anti-malarial treatment. However,

there was no evidence of residual *Plasmodium*-infected red blood cells in any of the CNS tissues at the time of death, and this suggests that it is unlikely that malaria is a major contributor to this patient's neurologic crisis. It is important to note that the underlying broncho-pulmonary infection, which may have progressed to the acute pneumonia detected at autopsy, could have existed before the ivermectin treatment was administered. It is possible that this condition has played a role in the development of the neurologic SAE. In addition, it is known that co-pathologies involving vascular changes in the lung and brain are sometimes seen in malaria infection. Besides malaria and pulmonary infection, one might also consider whether the patient could have had other concomitant infections, such as HIV infection, which could contribute to the development of the condition. As the patient was known to be in a relatively good state of health before treatment, it is unlikely that he had such an infection at the time of treatment.

The possibility of the patient being co-infected with *Onchocerca volvulus* should also be considered, and similarly whether such an infection, if present, might have facilitated the development of the neurologic signs and symptoms. The patient lived in an area meso-endemic for onchocerciasis,[7] and although he was not assessed for onchocercal infection it is unlikely that this particular filaria was a major factor in the development of this condition: the presentation and the epidemiology of PLERM is different from the Mazzotti-like reactions induced by the destruction of *Onchocerca volvulus* microfilariae and the release of *Wobachia* endosymbionts following ivermectin treatment.[3]

An atypical feature of the case is that, just after his admission to the hospital, the patient presented with abnormal movements evocative of a partial seizure. Such movements, which might result from a cerebral event, have rarely been reported in either DEC-, or ivermectin- induced *Loa* encephalopathies. This lack of a historical record might be due to the fact of these events being transient and thus may have been unobserved in previous cases.

The major pathologic changes in this case, other than the pulmonary pathology, were in the CNS. The vessel-associated accumulation of chronic inflammatory cells in the cerebral tissue together with deposits of hemosiderin pigment suggest that vascular damage may have been associated with the neurologic symptoms. The changes in the walls of some cerebral vessels—thickening of the basement membrane, disruption of the integrity of the vessel wall—were particularly marked. These changes, which could have been associated with a disruption of the BBB, may have either existed before the patient received ivermectin treatment or have developed following treatment. It is well known that ivermectin, when given at standard doses, does not penetrate into the brain in humans and most animal species, through the actions of P-glycoproteins present in the endothelial cells of the capillary vessels.[18] However, in certain animal groups, such as Grey Collie dogs and strains of mice harboring a mutation of the MDR1 gene, ivermectin can pass through the BBB. The latter animals, and humans who receive overdoses of ivermectin, develop signs of ivermectin toxicity, including mydriasis, vomiting, drooling, muscle fasciculation, apparent blindness, salivation, tachycardia, and hypotension.[19,20] Because the patient described in the present article did not show such signs and symptoms of ivermectin toxicity, it is more likely that his BBB was not altered at the time of treatment, and that its disruption occurred much later, probably when the blood concentration of ivermectin was low or zero.

A possible scenario for the pathogenesis of the patient's condition, given the available information, is that at the time of ivermectin treatment he harbored a *Loa* microfilarial load exceeding the threshold associated with the risk of post-ivermectin *Loa* encephalopathy. In addition, his tissues may have been already compromised by existing infection or pathology (possibly malaria and a broncho-pulmonary condition) inducing changes at the BBB level that facilitated the development of the neuropathologic condition. He then fell into a coma and developed complications (e.g., bedsores), which together with a worsening of the pulmonary pathology due to the coma and the difficulties of managing of the patient (e.g., tube-feeding), led to septicemia and death. This deterioration in his state could have also been facilitated by the depletion of his nutrition during the 2 months of hospitalization. Some days before his death, the patient refused to eat properly and this is likely to have hastened his demise.

It is interesting to compare this case of post-ivermectin *Loa*-encephalopathy with patients who died of spontaneous, or DEC-induced, *Loa* encephalopathies. The first reported case, which occurred in 1949, was a 40-year-old male living in the Bas-Congo province of the DRC, and whose history began with an abscess of the right popliteal fossa.[13] One week after the appearance of this abscess, he showed partial seizures of the arms, and then fell into a coma. The *Loa* microfilaremia measured at admission in hospital was 20,000 mf/mL, and the CSF contained many *Loa* mf. It is not known whether the patient had received DEC before developing the neurologic manifestations but the high microfilarial load makes this unlikely. The patient died 5 days after falling into a coma, and the autopsy findings included many chronic inflammatory cellular foci in the brain. In some instances these foci were associated with necrosis, small hemorrhages, the accumulation of brown granular pigment, and microfilariae present in giant cells. A second archival case,[21] was an expatriate who had lived in DRC and had a long history of loss of weight, dyspepsia, and repeated bouts of dysentery. He was admitted to the hospital after suffering violent headaches for several days. DEC treatment was started because he had a high *Loa* microfilaremia (noted as +++). During this treatment, his headaches worsened, and the patient complained of violent pain of left flank, mistiness of vision, and nausea. The DEC treatment was stopped on Day 4; however, the patient fell into a coma on Day 5 and died on Day 7. The majority of tissue changes described relates to peri-vascular cellular infiltrates with some mf lying free in the tissue or associated with small granulomas. These tissue findings are consistent with the present case.

The third reported case was a 38-year-old male expatriate who had also lived in DRC.[15] After first presenting with a general malaise and a flu-like syndrome, this patient complained of asthenia and generalized joint pains. The following day, he was disoriented, confused, and complained of visual impairment. At admission to hospital, he showed a marked disorientation, a somnolence, and had episodes of agitation, neck stiffness, and had a temperature at 37.8°C. No mf were found in the CSF; however, a fundus examination showed retinal hemorrhages and exudates, and the EEG showed diffuse abnormalities. His consciousness troubles lasted 5 days,

and then disappeared completely without any specific treatment. Several days later, an adult *Loa* parasite appeared under his palpebral conjunctiva; blood examination at this time showed a *Loa* microfilaremia of 74,000 mf/mL. One *Loa* mf was also found in a second CSF sample. DEC and corticosteroids treatment was started but 4 days later the patient fell into a deep coma that lasted for 7 days, and he then died. *Loa* mf were found in vessels of all the organs examined at autopsy, including many areas of the brain where many mf were seen usually associated with chronic inflammatory responses such as granulomas. Astrocytic changes were present in this case, as was necrosis and the presence of eosinophil leukocytes. This case, although having a number of characteristics similar to the present case, is clearly more severe and also showed a significant presence of parasites. The current case also differs markedly in time from original presentation to death.

The fourth and last published autopsy report of a *Loa* encephalopathy involves a 45-year-old male, again living in DRC who took "native medicine" to treat abdominal pain and fever.[22] Shortly thereafter, he became agitated and then fell into a coma. His temperature fluctuated between 37.5 and 40.0°C. A CSF sample was taken, which showed no abnormalities; no blood examination for parasites was performed. The patient died soon after, and the most significant autopsy findings were of *Loa* mf in fibrin thrombi obstructing the small vessels of all examined organs. Consistent with the present case, many of these vessels had thickened walls and were often surrounded by inflammatory cells and areas of micro-infarction with neurons undergoing degeneration.

Despite the obvious differences between all of these previous cases—some spontaneous, some chemotherapy-induced, the varying clinical presentations, and durations before death—there are similar aspects that suggest commonality in pathogenesis. An unexpected finding in the present patient was the fact that no mf were observed in any of the samples collected. This might be due to the fairly long interval between the treatment and the patient's death (54 days). The tissue changes in the brain involve inflammatory responses that implicate cells of the immune system; it is thus likely that immunologic status of the host is a significant factor in the pathogenesis of this condition.

The present findings raise many questions. What is the significance of pre-existing tissue changes? Why were parasites not found in the present study? Is there a specific clinical and pathologic sequence of events that related to this syndrome? It is difficult to answer these questions at this time given the paucity of data on the ivermectin-related events.[23] It is important to continue to investigate this condition to determine the best medical approach to preventing their occurrence and managing those unfortunately affected. A wider range of samples could be taken from future cases and thus provide more detailed information that could lead to better definition of the pathogenesis of this condition. For example, diagnostic tests for other possible infections (such as HIV, tuberculosis, and syphilis) and a wider selection of autopsy material. These cases are difficult to both manage and to obtain the samples necessary for intensive investigation due in part to the many challenges of practicing medicine in rural areas. The difficulties faced in diagnosis and interpretation in this present case hopefully encourage and guide those managing future cases to make every effort to gather as much diagnostic material and information as is possible. It is worth noting here that the careful and caring management of this patient during his illness was a major reason for his family's agreement for the autopsy to be carried out.

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