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Case Report

Silicon Foreign Body in the Cerebrum of a Rhesus Macaque (*Macaca mulatta*)

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A male rhesus macaque with a cephalic chamber implant for neurophysiology recording presented with hemiparesis affecting the left thoracic and pelvic limbs at approximately 5 wk after craniotomy surgery. MRI indicated a 1×2-cm ovoid cerebrocortical cystic lesion immediately subjacent to the right hemisphere craniotomy and recording chamber. Transdural aspiration of sterile transudate and resultant decompression resolved the hemiparesis, and follow-up MRI at 1 mo indicated resolution of the lesion. Subsequently, necropsy at study end revealed a cerebrocortical foreign body composed of silicon. The atypically slow cure rate of the lot of silicon used and the unique recording chamber configuration were underlying factors that contributed to the formation of this foreign body. To our knowledge, this report is the first description of iatrogenic intracerebral foreign body in a macaque.

Cephalic recording chamber implants are routinely used in neurophysiology research involving NHP. The chamber encases and protects craniotomies that provide access for the repeated transdural electrode placements necessary for studying the brain and behavior. In addition to providing access to the CNS, the chamber protects the underlying tissue from infection.[21] However, despite careful aseptic technique, cephalic implants are prone to infection. Undesirable outcomes associated with chamber infection range from superficial dural inflammation and accumulation of granulation tissue to meningitis and brain abscess. Complications associated with chamber infection directly affect animal welfare and are a primary reason for removal from study and interruption of research. These propensities prompted the Association of Primate Veterinarians to publish a guideline on chamber maintenance.[3]

Significant efforts to refine chamber maintenance protocols and improve chamber asepsis are documented in the literature. Modifications in postoperative maintenance, chamber cleaning procedures, and the use of dural sealants has improved outcomes by decreasing the incidence of infection and prolonging experiment duration.[1-3,10-13,16,17,20,21] For the past 10 y, our institution has used a sterile silicon elastomer (Kwik-Sil, World Precision Instruments, Sarasota, FL) to 'plug' the recording chamber and protect the underlying dura.[21] Our collective observations during this time period indicate that this approach has reduced the incidence of bacterial infections and dural granulation tissue formation. However, as we describe here, unexpected outcomes can occur when this approach is applied.

Case Report

A 7-y-old, intact, male rhesus macaque was engaged in a long-term neurophysiology study at the University of Arizona. The macaque was seronegative for *Macacine herpesvirus 1*, simian retrovirus type D, simian T-cell leukemia virus, and SIV and was tuberculosis-free as evidenced by multiple negative tuberculin skin test results. He was singly housed with intermittent grooming contact with a compatible male and had visual, auditory, and olfactory contact with 4 other male macaques in the animal housing room. The animal use protocol was reviewed and approved by the IACUC and performed in accordance with the Animal Welfare Act and Regulations, and Public Health Services Policy. The University of Arizona animal care and use program is AAALAC-accredited.

The macaque was captive-bred at the California National Primate Research Center and transferred to the University of Arizona in Spring 2014. He underwent behavioral training, presurgical brain imaging with MRI (results were normal), and in May 2015, was implanted with a cranial recording chamber under general anesthesia (isoflurane 1% to 2% in 100% oxygen) and by using strict aseptic technique. Analgesia (Buprenorphine SR 0.2 mg/kg SC; ibuprofen 10 mg/kg PO twice daily for 5 d) and antibiotic therapy (enrofloxacin 5 mg/kg PO daily for 5 d) were provided peri- and postoperatively. The recording chamber was unique in that a single circular chamber (diameter, 38 mm) was placed across the sagittal midline, enclosing 2 bilateral craniotomies (diameter, 14 mm each). The craniotomies were positioned over the frontal cortex for electrode access to the amygdala in both hemispheres. At the conclusion of the surgery, the dura was deemed intact, and sterile silicon elastomer was instilled into the chamber prior to capping.[21] The silicone product (Kwik-Sil, World Precision Instruments) is provided in a dual-syringe applicator that, once mixed, provides a liquid-state working time of less than 5 min. A firm set is achieved within 5 min, and setting is complete within 18 min.[24] No complications were evident during recovery.

Routine chamber maintenance began at 3 wk after surgery, approximately 1 wk before neurophysiology studies began. Sterile technique was always used when accessing the chamber.[17] Briefly, the chamber lid was removed, the silicon barrier was gently removed by using sterile forceps, and the chamber was flushed with approximately 500 mL of sterile 0.9% NaCl solution. Nothing abnormal was noted during this first chamber assessment: the silicon barrier was intact and easily removed,

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and the dura appeared undamaged. A small amount of fluid was present on top of the silicon barrier and was assumed to be transudate in light of its clear, light-yellow appearance and lack of odor. Because fluid accumulation is expected and typically present, neither cytology nor culture and sensitivity are routinely performed unless an infection is suspected. After chamber maintenance, silicon was reapplied and allowed to cure for 5 min, the chamber was capped, and the monkey was returned to its home cage.

In June 2015, the macaque presented with a seizure-like episode after the second postoperative chamber wash. The event was characterized by facial tics, eye blinking, and change in mentation lasting approximately 1 min. Clinical signs resolved without intervention, and the macaque returned to normal within 5 min. The initial assessment was provocative focal epileptic seizure induced by mechanical stimulation of the cortex during chamber wash.[5] Given the temporal proximity to neurosurgery, differential diagnoses also included infarct, hemorrhage, and infection. The macaque maintained normal clinical appearance, and no treatment was initiated at that time.

The following week, neurophysiology experiments were initiated in the right hemisphere craniotomy. Prior to each experiment, the chamber was flushed as described earlier, after which bupivicaine was applied to the dural surface to provide local anesthesia for electrode placement. The electrode drive was mounted onto the chamber, and a 23-gauge cannula was advanced 3 to 5 mm through the dura to provide guidance for the 32-gauge electrode. The electrode was slowly lowered to the right amygdala, the experiment performed, and the electrode and cannula were removed. The chamber was flushed again, and the silicon polymer reapplied to the dural surface.

At 16 h after the second neurophysiology session, the macaque presented with partial hemiparesis of the left thoracic and pelvic limbs. He grasped weakly with his left thoracic limb and could place but was nonweightbearing on his left pelvic limb. There was no facial involvement, vision appeared unaffected, and the patient could eat and drink without issue. Mentation and behavior were normal, with no clinical signs of pain (that is, normal posture, lack of head press, light tolerant, and so forth). Given the clinical presentation, recent history of surgery and seizure, and commencement of neurophysiology, the differential diagnoses remained as infarct, hemorrhage, and infection. Treatment was initiated immediately with NSAID (ibuprofen 10 mg/kg PO twice daily), additional analgesia in case of a headache (buprenorphine SR 0.2 mg/kg SC, ZooPharm Lab, Windsor, CO), and a third-generation cephalosporin (cefpodoxime 10 mg/kg PO daily). The chamber was visually evaluated for any indication of an underlying process, including the presence of infection. The chamber contained clear, light-yellow, nonodorous fluid. The dura in the right craniotomy had a small, pinpoint defect, consistent with cannulation the previous day. The chamber was flushed and resealed with silicon as described earlier after evaluation.

Abbreviated cageside and chair-restrained neurologic exams were performed at 48 h. The exams were performed without sedation and thus reflect what could be assessed with cooperation from the patient. Significant findings were limited to the left pelvic limb, which displayed decreased withdrawal in response to toe pinch and moderately increased patellar reflex, indicative of upper motor-neuron disease. The macaque demonstrated marginal improvement over several days after treatment was initiated. The left extremities remained paretic, but use of both limbs increased daily. Whether the increased usage was the result of adaptation by the patient or through clinical improvement was unclear. Otherwise, the macaque was stable, with normal mentation, good hydration and appetite, with no indication of clinical progression. Treatment continued with ibuprofen and cefpodoxime, the chamber was washed daily with enrofloxacin (0.2 mg/mL) in sterile 0.9% NaCl, and MRI was scheduled.

At 2 wk after the presentation of hemiparesis, 3-T MRI was performed under isoflurane general anesthesia. T1-weighted MRI indicated an ovoid cystic lesion measuring approximately 1×2 cm in the subcortical region immediately inferior to the right hemisphere craniotomy (Figure 1). The lesion was centered approximately 8 mm rostral to the central sulcus and 4 mm lateral to the sagittal sulcus. In the rhesus macaque brain, this cortical region is identified as the motor cortex, specifically the region controlling motor function to the lower extremities, trunk, and arm.[19] The cyst contained 2 hypointense fluid densities: one was consistent with a fluid of low cellularity; the other was a suspected semilunar foreign body in the dependent region of the lesion. In addition, blood was collected: the CBC count was within normal limits, and a comprehensive serum chemistry panel indicated a mildly elevated ALT (106 U/L; normal range 25 to 41U/L). Transient, clinically insignificant increase in ALT has been documented as a rare side effect of cefpodoxime administration in humans.[14] Muscle atrophy in the affected limbs might have contributed also.

The day after MRI, the macaque was sedated (ketamine, 6 mg/kg IM; midazolam, 0.1 mg/kg IM), and the chamber was accessed by using aseptic technique. The chamber was prepared with an alternating flush of sterile saline and dilute chlorhexidine solution and then draped. Sterile surgical gloves were applied, and transdural fine needle aspiration was performed in the right craniotomy by using a 25-gauge needle and 3-mL syringe. A single placement was performed; the needle was not redirected once fluid ceased to flow under light negative pressure. Approximately 0.5 mL of light yellow, slightly hazy fluid was aspirated and submitted for analysis. Cytology revealed a sterile eosinophilic modified transudate with a total protein concentration of 2.5 mg/dL and a total WBC count of 3300 cells per µL (14% neutrophils, 67% eosinophils, 19% mononuclear cells); Gram staining and aerobic culture of the aspirate were negative for microorganisms. On recovery from sedation, the macaque had immediate resolution of hemiparesis. Antibiotic therapy was continued, with careful monitoring for recurrence of clinical signs. The macaque remained stable, with clinically normal appearance.

MRI was repeated at 1 mo after initial presentation (Figure 2). The cystic lesion was reduced in size, with near-complete resolution of the fluid (transudate). The hypointense semilunar suspected foreign body was still evident. A neuroradiologist considered the lesion to be inactive, consistent with the complete resolution of clinical signs at this time. Third-generation cephalosporin (cefpodoxime) therapy was continued for a total of 2 mo. Given the high suspicion that the foreign body was silicon material, the silicon product used was evaluated for curing time. The working time of the lot used was prolonged to 20 min, compared with less than 5 min for other lots of the same product. The manufacturer confirmed that the product lot in inventory had a different curing time than described in the literature.

After veterinary and IACUC review of protocol endpoints and clinical condition, the macaque was allowed to continue on study with the stipulation of no further invasive procedures. Over the next 10 mo, the macaque participated in behavioral tasks only. The animal experienced 3 additional seizure events, 2 to 3 mo apart, similar to the first described. These were initiated

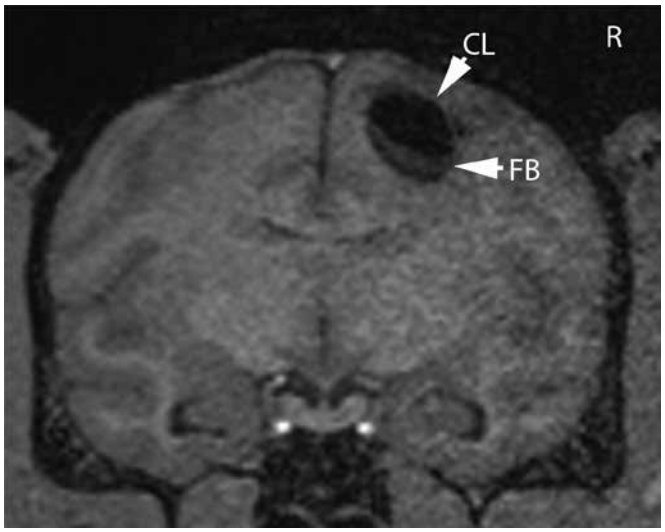

Figure 1. T1-weighted 3-T MRI, transverse section at the level of the amygdala, at 2 wk after onset of hemiparesis shows a hypointense cystic lesion (CL) and suspected semilunar foreign body (FB) in the right subcortical area subjacent to the craniotomy.

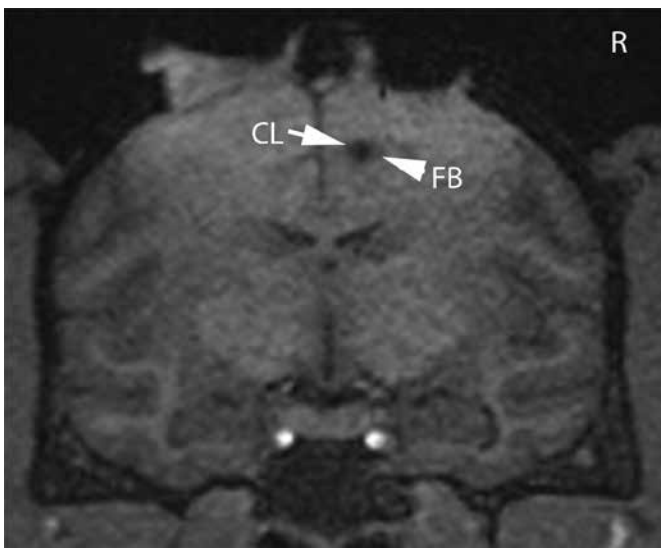

Figure 2. T1-weighted 3T MRI, transverse section at level of the amygdala, at 4 wk after fine-needle aspiration shows resolution of the cystic lesion (CL) and presence of suspected foreign body (FB).

by chamber wash and lasted no more than 1 min, with spontaneous resolution. Videorecording in the home cage was performed to determine whether spontaneous seizure activity occurred when no personnel were in the room. Four separate 8-h daytime intervals were assessed, with no abnormalities observed. Seizures were classified as provocative structural focal epilepsy induced by chamber wash.[5] Two complete physical exams with CBC count and comprehensive serum chemistry panel were performed in January and April 2016. There were no significant findings.

In May 2016, necropsy was performed after experimental endpoint. On gross exam, the dura was thickened over both craniotomies but not adherent to the cortical surface. Reflection of the dura on the right hemisphere revealed focally extensive cerebrocortical malacia with an intralesional silastic foreign body emerging through the cortical surface (Figure 3). The foreign body did not adhere to the cortex and fell free from the cavity, without manipulation, during sectioning. On sagittal

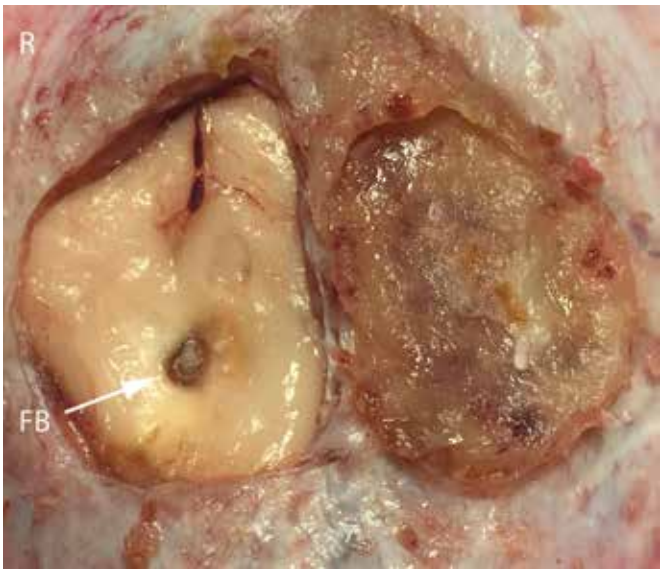

Figure 3. Dorsal view of the top of the brain extracted from the skull, with the dura removed from the right craniotomy site. The silicon foreign body is visible in the cortical defect (FB). The dura is intact over the left craniotomy site.

section, the cavity was evident subjacent to the motor cortex (Figure 4). The left cortical surface appeared normal. Histopathology of the brain tissue adjacent to the foreign body site revealed severe focally extensive cerebrocortical malacia with cavitation and multiple organized vascular thrombi (Figure 5). The dura mater showed severe diffuse lymphoplasmacytic and eosinophilic meningitis consistent with reactive tissue response. No bacteria were observed.

Discussion

Complications associated with chronic cephalic recording-chamber implants include infection, infarct, and hemorrhage. Several strategies have been developed to decrease the risk of complication, including the use of dural sealants such as silicon.[21] The prophylactic use of a dural barrier, in the current case, resulted in an iatrogenic cerebrocortical foreign body. We hypothesize that a defect in a specific product lot resulted in a prolonged curing time, and material entered the brain through the recording cannulation track before it hardened. In addition, we surmise the large chamber size, and thus the increased amount of silicon material required to cover the dual craniotomies, may have contributed to this incident. We suspect that after the second recording experiment, silicon entered the brain and caused the clinical signs observed on the following morning. This theory is supported by timing as well as the presence of a visible dural defect. There were no detectable defects noted during surgery, chamber flushes, or after the first recording experiment. The postoperative seizure event prompts consideration of 2 alternative scenarios. Perhaps seepage of silicon occurred prior to recording experiments, causing seizure but not motor impairment until the area was aggravated by electrode passage. Alternatively, the seizure events may have been unrelated. Seizures of this nature are not uncommon with activities that stimulate the cortical surface, such as chamber flush.

Cerebral foreign bodies in humans result predominantly from either penetrating trauma or neurosurgery (that is, hemoclips, sterile sponges). Clinical signs are varied and inconsistent, depending on the location and size of the lesion and the presence of infection. The most common complaint is headache,

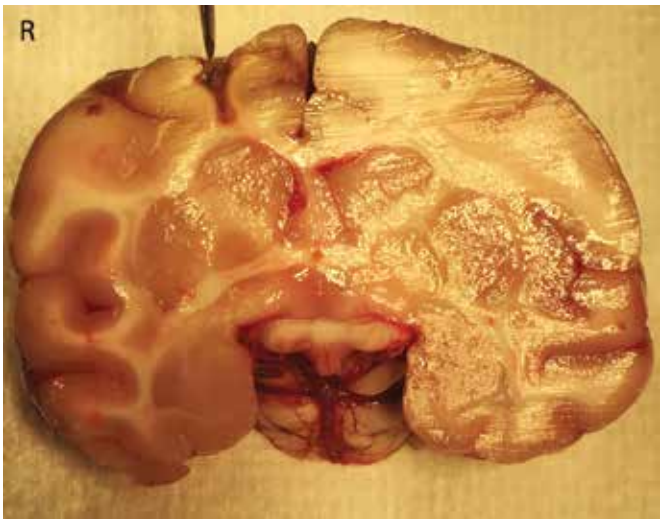

Figure 4. Transverse section of brain at the level of the amygdala at necropsy shows cerebrocortical cavitation after removal of foreign body (pointer).

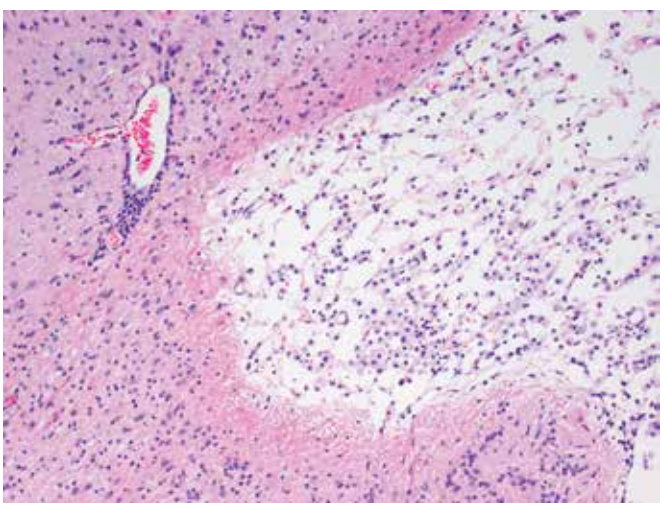

Figure 5. Histologic appearance of the cerebral lesion, demonstrating a large area of encephalomalacia with abundant glitter cells. Adjacent tissue displays marked gliosis and mild lymphocytic perivascular cuffing. Hematoxylin and eosin stain; total magnification, 25×.

although there are several reports of cerebral foreign bodies being an incidental finding, due to increased use of neuroimaging. Seizure and neurologic deficits may also be seen.[6] Fever and altered mentation are uncommon. Because clinical signs of intracerebral disease are nonspecific, additional diagnostics are required to differentiate cause. The leukogram is frequently normal in patients with brain abscess.[4,8,18] CSF analysis may aid in the diagnosis of infections but is not recommended when there is a space-occupying lesion in the brain, due to risk of herniation.[4,7-9,22] Intravenous contrast-enhanced CT is a useful diagnostic technique for excluding a space occupying lesion. However, when an intracranial mass is suspected, MRI is most sensitive for characterization and classification.[4,18] Therefore, advanced imaging is critical for localization and differentiation, but this modality is not always available in the laboratory animal environment.[15,23]

Prior to MRI, we did not suspect a foreign body in our patient. Treatment was initiated based on a presumption of infection (with or without hemorrhage and/or infarct), which is a known and common complication of this experimental model.[15] If infection is suspected in the absence of immediate neuroimaging, rapid empirical treatment is necessary. In humans, antibiotic therapy is initiated as soon as brain abscess is considered in the differential diagnosis, until advanced imaging and surgical intervention can be performed.[4,7-9] Brain abscess associated with neurosurgery is most commonly due to *Staphylococcus* or *Streptococcus*. Recommended empirical treatment thus includes a 3rd- or 4th-generation cephalosporin plus metronidazole parenterally for 2 to 8 wk.[7-9,15,18] In our case, access to MRI was delayed 2 wk due to its offsite location, accompanying logistic challenges, and shared human clinical use. Oral cefpodoxime was initiated immediately, and we considered parenteral antibiotic administration. However, given the relative stability of the patient and the challenge of multiple sedations for intravenous dosing, we did not pursue parenteral treatment in this case. Metronidazole therapy was not considered at the time of clinical presentation but will be included in the future when brain abscess is suspected. However, oral metronidazole formulations are distasteful, and patient compliance may be an issue regarding long-term administration.

Once a cerebral lesion is identified and localized by using imaging, neurosurgical aspiration is recommended. Aspiration allows for direct biopsy as well as decompression. In human cases of brain abscess, medical management alone results in worse outcomes than those approached surgically.[8,9] In the current case, aspiration achieved immediate resolution of hemiparesis. This resolution of significant clinical signs and the observation of only 4 seizure-like episodes despite intensive video monitoring allowed the macaque to remain on the behavioral study until the originally scheduled endpoint. The superficial location of the lesion in our patient, coupled with the ability to access it through the existing chamber and craniotomy, made aspiration a relatively simple procedure. Deeper, subcortical lesions may require stereotaxic surgery to ensure appropriate targeting.[8] Seizure, although possible with intracerebral lesions, should be managed symptomatically, given that prophylactic antiseizure medication has not been shown to reduce occurrence, at least in patients with brain tumor.[8,9,22] Corticosteroids should be reserved for patients with severe cerebral edema and eminent brain herniation.[7-9,18]

This case represents an unusual complication associated with an implanted cephalic recording chamber. Advanced imaging was critical to correct diagnosis and treatment in this case, although we recognize that this modality may not be available in all cases. The exact pathogenesis underlying the formation of the foreign body is unclear but likely involves a defective lot of silastic material with delayed solidification combined with a unique chamber design that was used exclusively on this subject. To our knowledge, this report is the first description of iatrogenic cerebrocortical foreign body and its clinical management in a rhesus macaque.

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