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Case Report

Granuloma Due to Oxidized Regenerated Cellulose in an Aged Rhesus Macaque (*Macaca mulatta*)

Marie-Josee MF Lemoy,[1,*] Angela Colagross Schouten,[1] and Don R Canfield[2]

Bioabsorbable hemostatic agents such as oxidized regenerated cellulose are widely used to control intraoperative diffuse capillary bleeding. Compared with electrocautery or ligation, oxidized regenerated cellulose has the advantage of controlling bleeding without occluding the vessel lumen or causing thermal injuries to adjacent tissue. Although the manufacturer recommends removal of the material once hemostasis is achieved, oxidized regenerated cellulose is a bioabsorbable hemostatic agent and is often left in the surgical bed to prevent subsequent bleeding after surgical closure. However, noninvasive imaging techniques have revealed granulomatous foreign-body reactions that mimic infection or tumor recurrence. We present a case report of sterile peritonitis and granuloma formation secondary to the presence of oxidized regenerated cellulose after intestinal resection to excise a colonic adenocarcinoma in an aged rhesus macaque.

Bioabsorbable hemostatic agents such as oxidized regenerated cellulose (for example, Surgicel) are widely used to control intraoperative diffuse capillary bleeding. Compared with electrocautery or ligation, oxidized regenerated cellulose has the advantage of controlling bleeding without occluding the vessel lumen or causing thermal injuries to adjacent tissue.[16]

Oxidized regenerated cellulose is formed by dissolving the α-cellulose of decomposed wood pulp in an alkaline solution and subsequently regenerating it as a continuous fiber. This fiber is then woven into a gauze and oxidized.[17,22] Oxidized regenerated cellulose is supplied as a substrate that is flexible, malleable, and trimable.[16]

The mechanism of hemostasis of oxidized regenerated cellulose is reportedly associated with its caustic activity.[2] The oxidation of cellulose produces a low-pH organic acid that reacts with blood, thus forming an artificial clot and causing platelet aggregation.[18]

Although the manufacturer recommends the removal of oxidized regenerated cellulose once hemostasis is achieved,[8] the product, a bioabsorbable hemostatic agent, is often left in situ within the surgical bed to prevent bleeding after surgical procedures. The biodegradation and elimination of oxidized regenerated cellulose from the tissue occurs in 2 phases.[14] Polyanhydroglucuronic acid, the major functional unit of oxidized regenerated cellulose, is readily soluble. This acid is degraded extracellulary and systematically cleared from the system approximately 18 h after implantation.[13,14] The remaining fibrous residue, however, requires macrophage phagocytosis for clearance and can be observed within macrophages for at least 48 h after implantation.[13] Unfortunately, these fibrous residues have a prolonged degradation, and their persistence for as long as 7 mo after surgery has been confirmed histologically.[7]

Despite the biocompatibility of oxidized regenerated cellulose, granulomatous foreign-body reactions that imitate infection or tumor recurrence have been revealed by using noninvasive imaging techniques.[1,11,12,15,17,18,22] Here we describe a case of peritonitis and granuloma formation secondary to the presence of oxidized regenerated cellulose after an intestinal resection to excise a colonic adenocarcinoma in an aged rhesus macaque.

Case Report

A female rhesus macaque (age, 17 y 7 mo; *Macaca mulatta*) was presented to the hospital for weight loss and diarrhea. This colony-bred animal had no pertinent previous medical history. The macaque was assigned to a soy-milk–formula project at birth (0 to 5 mo), raised in a nursery, and later assigned to our outdoor SPF breeding colony. This animal was reproductively active; she conceived and delivered 8 offspring. Few occurrences of nonpathogenic diarrhea and trauma were noted in the 8 y prior to this presentation. At the time of presentation, the macaque resided at the California National Primate Research Center, an AAALAC-accredited facility, in an outdoor SPF breeding colony. All animals in this enclosure were maintained according to the *Guide for the Care and Use of Laboratory Animals*.[10] Protocols for the maintenance and breeding of rhesus macaque colonies were approved by the University of California IACUC. The animal had not undergone any experimental procedures during the 17 y prior to this initial presentation.

On initial presentation, the macaque was bright, alert, and responsive , with no obvious sign of discomfort; she was sedated with ketamine (10 mg/kg IM; Mylan Institutional, Rockford, IL), and a complete physical examination, whole-blood analysis (NOVA-CCX Stat Analyzer, Nova Biomedical, Waltham, MA), hematology, serum biochemistry profile, rectal culture, stool parasitology, and fecal occult analysis were performed.

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Departments of [1]Primate Medicine and [2]Pathology, California National Primate Research Center, University of California, Davis, California.
[*]Corresponding author. Email: mjlemoy@primate.ucdavis.edu

Clinical examination revealed the presence of a firm mass (3 cm × 4 cm) in the cranial right quadrant of the abdomen. The cecum was distended with the presence of granular material. The animal was thin (7.9 kg), with a body condition score of 1.5 out of 5,[20] and had lost 15.5% of her previous body weight (9.3 kg), which was obtained 5 mo earlier. Body temperature, heart rate, and respiration rate were within normal limits; no other abnormalities were found on physical examination.

Inhouse, immediate whole-blood analysis demonstrated mild anemia and electrolyte imbalance. The macaque was mildly hyponatremic (137.4 mM/L) and hypokalemic (3.76 mM/L), with a Hct of 31%. Hematology results confirmed the presence of a mild microcytic, hypochromic anemia and were consistent with chronic blood loss. The Hct was 28.5%, with a MCV of 65 fL, MCH of 19.2 pg, and MCHC of 29.4 pg/fL. A blood smear revealed hypochromasia. Hypoproteinemia also was noted, with a total protein of 6.0 mg/dL. The differential analysis revealed a moderate eosinophilia of 13%. All other parameters were within normal limits.

Serum biochemistry analysis demonstrated electrolyte imbalances similar to those on the inhouse whole-blood analysis and confirmed the hypoproteinemia (5.3 g/dL) and hypoalbuminemia (2.4 g/dL). The rectal culture was devoid of common pathogenic bacteria, and stool parasitology only demonstrated the presence of opportunistic trichomonas. The fecal occult series was positive, indicating chronic intestinal blood loss.

The macaque was given subcutaneous isotonic fluid therapy (lactated Ringers solution, 40 mL/kg SC; Baxter Health Care, Deerfield, IL) to correct the electrolyte imbalance, and tylosin (20 mg/kg IM for 10 d; Elanco Animal health, Indianapolis, IN) was started as an empirical treatment for nonpathogenic diarrhea. A presumptive diagnosis of ileocecocolic adenocarcinoma was made, and the macaque was scheduled for exploratory laparotomy, with possible resection of the mass.

Nine days after presentation, the macaque was fasted and received Golytely (30 mL/kg PO; Braintree Laboratories, Braintree, MA) to cleanse the gastrointestinal system in preparation for exploratory laparotomy for a suspected gastrointestinal adenocarcinoma. The following day, the macaque was weighed (7.5 kg), sedated (ketamine 10 mg/kg IM), given atropine (0.05 mg/kg IM; Baxter Health Care, Shawnee Mission, KS), intubated, and maintained on isoflurane (1.5% to 2%; Piramal Critical Care, Bethlehem, PA). The abdomen was surgically prepared. Exploration of the abdomen revealed complete adhesion of the cecum to the abdominal wall, liver, and pancreas. Blunt dissection of the adhesion was attempted, but the liver and pancreas had persistent capillary oozing from the damaged area that was inadvertently created during dissection. Bleeding could not be controlled with manual pressure, and the surgeons were reluctant to use electrocautery on the tissue. Therefore, a small band, approximately 1 × 2 cm, of oxidized regenerated cellulose was applied to the liver and pancreas to control bleeding and left in place. A firm ileocecocolic mass was identified, and resection of the ileocecocolic junction was performed. Anastomosis of the ileum and the ascending colon was achieved with polyglycolic acid suture (4-0, Ethicon, Sommerville, NJ) in a simple interrupted suture pattern. The abdomen was then flushed with 2 L of warm sterile saline. Finally, the abdomen was inspected, and hemostasis was confirmed. The abdominal wall and skin were closed in a standard continuous pattern with polyglycolic acid suture (Ethicon). The ileocecocolic mass was placed in10% buffered formalin and submitted for histopathologic analysis.

Post operatively the animal received oxymorphone (0.3 mg/kg IM every 8 h for 3 d; Endo Pharmaceuticals, Chadds Ford, PA), metronidazole (50 mg/kg SC daily for 10 d, US Compounding Veterinary Pharmacy, Conway, AR), enrofloxacin (5 mg/kg IM every 12 h for 10 d; Bayer Health Care), cefazolin (25 mg/kg IM every 12 h for 7 d; Steri-Pharma, Syracuse, NY) and maropitant (1 mg/kg SC daily for 5 d; Pfizer Animal Health, New York, NY). At 10 d after surgery, the macaque was stable, with a good appetite and producing normal stool. She had gained approximately 0.5 kg (body weight, 8.0 kg), and the incision was healing well. The macaque was then discharged and returned to the outdoor enclosure.

Histologic evaluation of the ileocecocolic mass revealed significant chronic active inflammation in the lamina propria, including lymphocytes, plasma cells, and numerous polymorphonuclear cells (both neutrophils and eosinophils), with several lymphoid patches in all areas. At the junction of ileum and cecum, the mucosa was thinned or ulcerated, and the epithelium displayed typical features of adenocarcinomatous transformation, which appeared to be confined to the mucosa, with incursions into but not through the muscularis mucosae. The section of proximal colon had 2 areas where only slightly abnormal-appearing mucosal epithelium extended into (but not through) the muscularis mucosae. The diagnosis was adenocarcinoma in situ.

One month later, the animal was brought to the hospital for lethargy. On presentation, the animal was alert and responsive but was slow-moving; she was sedated with ketamine (10 mg/kg IM) and dexmedetomidine (15 mcg/kg IM, Pfizer Animal Health). A complete physical exam, whole-blood analysis, hematology, serum biochemistry profile, abdominal radiography and ultrasonography, and culture and cytology of abdominal fluid were performed.

Physical examination revealed a distended abdomen, 14% weight loss (6.8 kg) from the previously recorded weight, and mild fever (102.1 °F). The inhouse immediate whole-blood analysis was unremarkable except for a mild anemia (Hct, 30%). Hematology revealed a leukocytosis (WBC, 23.1× 10^3/µL), with 80% neutrophils although the fibrinogen was only mildly elevated (300 mg/dL). Hematology results denoted a moderate hypochromic, microcytic anemia (Hct, 22.7; MCV, 51 fL). The serum biochemistry profile indicated severe hypoalbuminemia (albumin, 1.7 g/dL) with a normal total protein (7.3 g/dL) and hypoglycemia (glucose, 28 mg/dL). Abdominal radiography (Figure 1) revealed a diffuse loss of detail among the abdominal viscera that was compatible with ascites. A mass effect in the left caudal quadrant of the abdomen, with displacement of intestinal loops to the right, was noted also. Abdominal ultrasonography confirmed ascites, with the presence of free fluid around the liver and kidney. In addition, a fluid-filled cystic structure was present in the caudal abdomen. An ultrasound-guided aspiration of both the abdominal fluid and cystic structure produced milky fluid, which was submitted for cytology. Cytology of the fluid from the abdomen and cystic structure demonstrated a moderate amount of background staining and the presence of neutrophils. No bacteria were found in the samples. The abdominal-fluid culture was negative for aerobic and anaerobic bacteria.

Due to the poor prognosis and suspicion of peritonitis, the animal was euthanized by using an overdose of pentobarbital

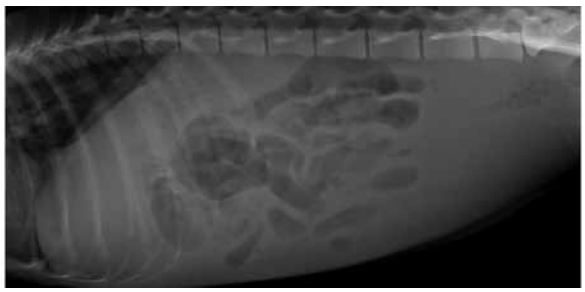

Figure 1. This radiographic lateral view of abdomen shows diffuse loss of detail among the abdominal viscera that was compatible with ascites.

(0.25 g/kg IV, Vortech Pharmaceuticals, Dearborn, MI). At gross necropsy, the macaque was markedly thin and dehydrated due to what appeared to be an extensive fibrinopurulent peritonitis, with numerous adhesions among viscera and many 'pockets' of thick, pale tan to white exudate. The site of intestinal anastomosis appeared to be healthy and intact, but the entire gastrointestinal tract was thickened, with numerous firm fibrinous adhesions between bowel loops and between bowel and adjacent abdominal viscera. An ill-defined but irregularly oval, soft to spongy, tan to white mass in the left caudal abdomen displaced adherent intestinal loops to the right. Lymph nodes associated with the gastrointestinal tract were prominent to enlarged. Additional findings included mild pulmonary congestion and edema, with multifocal pleural adhesions and black pinpoint stippling of the pulmonary parenchyma, and the tracheobronchial lymph nodes were discolored black. Histopathologic examination of selected tissues revealed a diffuse, chronic–active, peritonitis–serositis comprising infiltrates of lymphocytes, plasma cells, neutrophils, histiocytes, and microhemorrhage on a background of proliferating fibroblasts. The abdominal mass lesion was composed of similar inflammatory components peripherally, with a larger central area of more extensive fibrosis containing longitudinal and cross sections of amphophilic to unstained interlacing fibers that were surrounded and being engulfed by numerous multinucleate giant cells; these findings are consistent with an extensive and localized granulomatous response to foreign material (Figure 2).

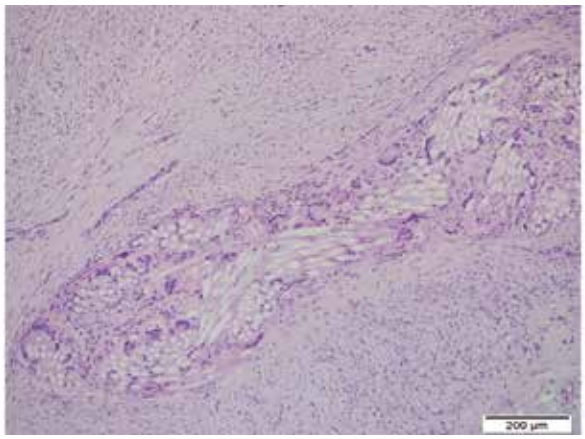

Figure 2. This photomicrograph of a representative section of the abdominal mass show longitudinal and cross sections of amphophilic to unstained interlacing fibers surrounded and being engulfed by numerous multinucleate giant cells on a background of fibrosis—an extensive and localized granulomatous response to foreign material.

Discussion

The presence of granulomas and the migration of oxidized regenerated cellulose mimicking tumor recurrence or metastasis on imaging have been reported in the human literature.[1,4,5,11,12,17,18,22] To our knowledge, this current report is the first description of granuloma formation secondary to surgical placement of oxidized regenerated cellulose in an NHP.

In this case, relocation of the oxidized regenerated cellulose, which had been left in situ over the liver and pancreas, was noted. Both fibrous residues ingested by macrophages and the fibrous mass itself were found in the caudal abdomen. Even though migration might have occurred, as has been described in other case reports,[3,5,6] in which residues of oxidized regenerated cellulose migrated from the site where they were placed to the spinal column, we suspect that the oxidized regenerated cellulose in the current case was displaced during the lavage of the abdomen at the end of the surgery.

In the previous published cases,[21,22] granulomas due to oxidized regenerated cellulose have not been associated with bacterial peritonitis. This outcome is likely due both to rigorous maintenance of the sterile surgical field and to the fact that oxidized regenerated cellulose is considered bactericidal[19] against a wide range of aerobes, anaerobes, and gram-positive and gram-negative bacteria. In animal studies, oxidized regenerated cellulose did not enhance infection in vivo.[8,19] However, sterile peritonitis or abscesses caused by oxidized regenerated cellulose residues have been described.[8,21] Similarly in the case we describe here, the macaque developed a sterile peritonitis or abscess subsequent to the presence of oxidized regenerated cellulose within the abdomen. The culture of the abdominal fluid collected during ultrasound was negative, and the cytology did not demonstrate the presence of bacteria. The hemogram collected during the second hospitalization was inconclusive but did not reveal the typical presentation of bacterial peritonitis: there was no left shift nor signs of toxic granulation, and the fibrinogen and total protein concentrations were within normal limits.

At gross necropsy, the intestinal anastomosis site was intact and watertight and appeared healthy. The abdomen, however, contained what appeared to be a purulent peritonitis centered around a poorly delineated, very soft, pale tan to almost white, mass lesion in the lower abdomen. Histologic examination revealed a granulomatous reaction, devoid of bacteria, but rather targeting scattered aggregates of interlacing, empty-appearing, 'ghost' fibers in both longitudinal and cross sections, an appearance characteristic of oxidized regenerated cellulose,[15] with the overall picture consistent with a particularly vigorous foreign-body reaction.

Risk factors contributing to the formation of granulomas to oxidized regenerated cellulose are unclear. Some authors have associated these lesions with the presence of a chronic inflammatory reaction,[12,17] whereas others have proposed that the acidic character of oxidized regenerated cellulose increases inflammation in the surrounding tissue.[22] In addition, various unknown factors that might trigger such a reaction in some subjects.[11] Nonetheless, even though oxidized regenerated cellulose is only weakly antigenic, the product remains a foreign body that can stimulate the immune system. Therefore it is reasonable to hypothesize that any of the material that is left in situ may predispose to a foreign-body reaction.

In conclusion, oxidized regenerated cellulose, when used correctly, is an exceptional and crucial tool for the reliable and secure control of minor bleeding during surgery. Adverse reactions should be considered and included among possible diagnoses when an unusual mass lesion is found after a surgery during which oxidized regenerated cellulose was left in situ.

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