Hemostasis after partial hepatectomy using argon beam coagulation and a concentrated albumin

Hua Xie [a], Ronald F. Wolf [b], John Petty [c], Allen Burke [d],
Jeffery S. Teach [a], Kenton W. Gregory [a], Scott A. Prahl [a]

[a]Oregon Medical Laser Center, [b]Department of Surgery, Providence St. Vincent Medical Center, Portland, OR; [c]Oregon Health Sciences University, Portland, OR; [d]Armed Forces Institute of Pathology, Washington, DC

ABSTRACT

Background: The argon beam coagulator (ABC) is frequently used to control bleeding on parenchymatous organs during surgery. The purpose of this study was to assess whether it improves the efficacy of hemostasis of using the argon beam coagulation with a concentrated human albumin at partial hepatectomy.

Methods: Thirty-two domestic swine were randomized and treated with either conventional argon beam coagulation alone (ABC, N=16) or the argon beam coagulation in association with a concentrated human albumin (ABCA, N=16) following by wedge resection of left median lobe of the liver using a digital fracture technique. Postoperative followup was up to 90 days for acute parameters and chronic bio-compatibility studies.

Results: The ABCA group required fewer repeat applications of argon beam coagulation than ABC alone group (mean 0.5 vs. 1.5, p=0.007). The total blood loss of ABCA was significantly less than ABC group (mean 3.83 vs. 8.29, p=0.049). The post-operative reaction was similar to the both groups, which shows a chronic inflammation response as part of the ongoing normal healing process.

Conclusions: We demonstrated that the ABCA is more effective and reliable than ABC alone in hemostasis of hepatic injury. Clinical trials of using the ABCA for solid organs injury repair are warranted.

Keywords: Liver, Hemostasis, Coagulation, Thermal Effect

INTRODUCTION

The primary difficulties in liver surgery are achieving initial hemostasis and reducing postoperative exsanguinating hemorrhage or rebleeding. Present techniques, such as suture, mess packing and tissue gluing commonly fail in liver surgery due to limitations such as diffuse oozing, poor tissue adhesion and inadequate physical and environmental conditions (2,8). Several electronic devices, such as electrocautery, microwave, lasers, focus ultrasound and radiofrequency are used to fuse tissue and small vessels by generating a thermal process to achieve hemostasis. However, these devices had limited to success in a large resection of solid organs (1,13,17,18).

Using an albumin solder with an 800nm pulsed laser to repair liver injures has been described in our previous studies (19). The results showed that the concentrated albumin solder with the laser provided excellent hemostasis on liver injuries.

The argon beam coagulator is a common device in most surgical units and is frequently used in surgery for bleeding control (10). The argon beam coagulator is a noncontact, monopolar electrocoagulation device that transmits radiofrequency electrical energy from a hand-held electrode across a jet of argon gas. The argon gas jet clears the field of pooled blood and evenly distributes electrical energy to the target tissue. However, a safety consideration, "the possibility that the flow of argon gas onto bleeding tissue may cause venous gas embolism, which may be fatal." has been warned (5). This study was designed to improve the efficacy of ABC. We assumed that using the concentrated albumin coating with ABC (ABCA) would not only seal hemorrhage surface, but would also prevent gas entering the open venous system of the injury liver. Preliminary experiments have demonstrated the feasibility and advantages of the ABCA procedure in the anti-coagulation pig model (20). This study explored further for the safety and reliability of ABCA.

MATERIALS AND METHODS

Thirty-two juvenile domestic swine (body weight from 30 to 40 kg) were divided into two groups that received either ABC (n=16) or ABCA (n=16) treatment. All experiments were performed in accordance with the *1996 National Research Council Guide for the Care and Use of Laboratory Animals* and applicable federal regulations.

Surgery*:* Domestic swine were numbered and correctly identified on the day of operation. Twenty minutes prior to operation, each animal was given 500 mg of intravenous Cefotetan and a 250 ml fluid bolus of Ringer's Lactate. Anesthesia was induced with 4-9 mg/kg of intramuscular tiletamin / zolazepam, followed by isoflurane by mask and endotracheal intubation. The right femoral artery was surgically isolated and cannulated with a 6 Fr catheter to facilitate continuous blood pressure monitoring and retrieval of blood for laboratory studies. Vital indices and O_2 saturation and CO_2 pressure were monitored during surgery. Preoperative lab studies included a blood count, liver function tests, and an activated clotting time (ACT). The animals were given 5000 units of heparin intravenously before surgery. Approximately 10 minutes later, the ACT was checked, and if it exceeded 200 seconds, the operation proceeded. If the ACT were shorter than 200 seconds were, additional heparin would be given. The operation proceeded with a vertical midline incision to enter the abdomen. The left median lobe of the live was exposed. A non-anatomic resection of the inferior aspect of this lobe was performed. The resection size was selected so that the raw surface of liver parenchyma was similar for all injures. The liver capsule was scored with cautery, the parenchyma was fractured with hemostats, and vessels larger than 5 mm were ligated. Imprints of the resected segment were obtained to measure the surface area.

Each animal was randomized to either ABC or ABCA treatment. Randomization was stratified to encourage animals in each group to undergo surgery on the same day. Typically, 1 or 2 animals in each group would be resected on a given day. Animals in the ABC group received coagulation (Argon Beam Coagulator, Volleyball, Boulder, CO) in the "fulgurate" setting at 75 W with an argon flow rate of 4 liter / minute. This was applied to the raw surface while proximal digital compression was applied. No hepatic vascular control was employed. Animals in ABCA group received similar application of argon beam coagulation. However, prior to coagulation, the raw surface of liver resection was painted with a layer of 38 % human albumin. The albumin layer was then "soldered" to the liver surface using the argon beam coagulator. The volume of albumin used was recorded. In both groups, once gross hemostasis was initially achieved, the resected surface was packed with gauze for three minutes, the resected surface was then inspected. if hemostasis was not complete, the animal received reapplication of ABC or ABCA in accordance with its randomization assignment. The liver surface was again packed with gauze for three minutes. The process was repeated until hemostasis was complete. Once hemostasis was completed, the liver was packed with gauze for a final ten minutes. The liver surface was inspected and the abdomen was closed without drains. Measurements of number of vessels ligated, surface area of liver resection, time of treatment, blood lost on gauze packs, and number of episodes of hemostasis and repacked were recorded.

Postoperatively, the animals were returned to their pens after waking from anesthesia and allowed to resume ad libitum feeding. Fentanyl patches were applied for analgesia. They were monitored for jaundice, fever, abscess, respiratory failure, ascites, loss of appetite and wound complications. Postoperative antibiotics were not administrated. The animals were euthanized at 0 day (n=11, 6 in ABC and 5 in ABCA), 30 days (n=10, 5 in ABC and 5 in ABCA), 90 days (n=10, 5 in ABC and other 5 in ABCA) following surgery. The postsurgical adhesion score was evaluated by grossly examining the abdominal cavity (3), and the sign of infection was examined at time of euthanization. The liver specimens then were harvested for histopathological examinations.

Concentrated albumin: 25% commercial human serum albumin from our hospital pharmacy was concentrated to 38 % weight / volume using a pressure filtration chamber (Model 8400, YM 30 filter, Amicom, MA) under 35-45 psi at room temperature. The refractive index was measured to confirm the final concentration. The 38 % albumin was drawn into syringes, sterilized by gamma irradiation, and stored at 4 ^{0}C until use.

Statistics: All data are expressed as mean ± standard deviation. The results from comparison of parametric data were analyzed by unpaired *t* test. Mann-Whitney U test used to analyze differences in numbers of rebleedings and adhesion scores. Pre- and post-op ACT was examined by paired *t* test. P values < 0.05 was considered statistically significance.

RESULTS

The vital indices, O_2 saturation and CO_2 pressure remained normal during either ABC or ABCA in all animals. One animal in ABC group died several hours postoperatively. Subsequent necropsy showed major intraabdominal

Table 1: The comparison of ACT (Mean ± SD, t-Test)

	ABC (n=16)	ABCA (n=16)	p-value
Pre-op ACT (units)	281 ± 57	290 ± 95	0.421
Post-op ACT(units)	240 ± 44	221 ± 38	0.778
p-value	0.027	0.056	

hemorrhage from the liver. One animal in ABCA group had to be sacrificed due to a fascial disruption of his abdominal closure at day 4 after surgery, and was found to have some small nodules on the serosa of his ileum. They both were excluded from this study. Of the 30 remaining animals, 15 were received ABC treatment and other 15 were received ABCA treatment. In ABC group, 5 animals were sacrificed at day 0, 5 were at day 30 and, 5 at day 90. In ABCA group, same numbers of animal were sacrificed at same study periods as ABC group.

The remaining 30 animals did well postoperatively. Their body weight increased as usual after surgery. All general laboratory indices indicated normal as well as the indices of liver function (data was not shown). Animals were heparinized with 5000 units heparin intravenously before surgery. The ACT remained above 200 during the operations. At time of hemostasis achieved, the ACT decreased slightly. The ACT level showed no differences between ABC and ABCA groups (see Table 1). The experimental data of two groups are compared in table 2. There were no significant differences between ABC and ABCA groups in number of ligated vessels and surface area of liver resected. In ABCA group, the animals had similar amounts of albumin applied, with a range of applied albumin volume from 1.2 to 6.8 ml. Time spent using the ABC as significantly longer for the ABC group than the ABCA group.

Table 2: A summary of ABC and ABCA treatment (Mean ± SD)

	ABC (n=15)	ABCA (n=15)	p-value
Surface area of resection (cm sq.)	12.6 ± 2.7	12.7 ± 2.5	0.911
Number of vessels ligated	5.7 ± 1.7	6.1 ± 1.3	0.527
Argon time (seconds)	154 ± 59	103 ± 42	0.010*
Time to complete hemostasis (minutes)	16.7 ± 6.2	16.1 ± 8.2	0.835
Blood loss (ml)	8.3 ± 7.0	3.8 ± 2.7	0.049*
number of rebleedings	1.50 ± 1.0	0.5 ± 0.6	0.007*
Adhesion Score	3.8 ±1.4	3.4 ± 1.9	0.918

Mann-Whitney U Test, t-Test; * Significant difference

longer than the time spent in ABCA group (mean 154 vs. 103, p = 0.01). However, the total time of complete hemostasis was similar between the two groups (mean 16.7 vs. 16.1). The number of episode rebleedings and blood loss on used packing sponges was significantly higher in ABC group (p = 0.007 and 0.049).

Gross examination at day 0 indicated that a carbonized tissue coating was present on the surface of liver after coagulation. The layer of carbonized tissue at ABCA treated liver appeared harder and thicker on the surface (Figure 1, 7). A mild local tissue adhesion to wound site was noted at both groups at day 30 and 90 (Figure 3). There was no difference in adhesion score between the groups (mean 3.80 vs. 3.44, p=0.918).

Histology showed similar thermal effect on liver resection after ABC (Figure 4) and ABCA (Figure 7) treatment at day 0. The liver through the treatment area showed surface coagulation necrosis, which overlies an area of hyperemia. The liver surface characterized by a mixture of cauterized albumin, red cells, and fibrin-platelet thrombus. The extent of surface/tissue injury is 2 – 3 mm in thickness (Figure 4,7). At day 30 after surgery, the repaired site showed an abscess cavity lined by fibrous tissue within an incision of the liver with fibrous tissue on the surface sealing the defect in both treatments(Figure 5). The center of the abscess contains the inflammatory cells, necrotic liver, and a granulomatous reaction to bile and albumin, which surrounded by chronic lymphoid response (Figure 8). At day 90 post-operatively, localized adhered omentum healed over the liver raw surface (Figure 3). The hepatic lobules adjacent to the omentum demonstrated regeneration with minimal fibrosis or inflammation (Figure 6, 9). The inflammation was walled by marked fibrous reaction with focal ossification, which related to a little giant cell reaction with lymphoid hyperplasia. The adjacent liver parenchyma is uninvolved, without significant inflammation or scarring (Figure 6).

DISCUSSION

Surgery of solid visceral organ like liver, spleen and kidney has always proved to be challenging, not only in immediate hemostasis, but also in preventing complications of post-surgery. Exsanguination is one of the most common and dangerous complications. The patient undergoing liver surgery, who had blood coagulation function failure due to primary liver disease or severe visceral organ injury complicated with abdominal trauma, has a high risk of morbidity and mortality (4). Rapid and effective "sealing" of the injury site is a key of accomplishing these surgeries. Most of traditional surgical techniques, known as gauze packing, mesh sutures and staples, fail to "seal" the resected surface. Topical hemostatic agents such as fibrin glue and microcrystalline collagen powder have been found to be effective in controlling oozing from liver raw surface. The postoperative morbidity and mortality rates was reported at 45% and 13% in collagen powder, 39% and 10% in fibrin glue in 62 patients of elective hepatic resection (9). Some reports warned that they might cause fatal allergic reaction to the glue components in deep hepatic wound (7,12). Electrocautery and lasers are common surgical tools that provided a convenient method for handling active bleeding at surgical field. However, when faced with large vessels and complex wound, especially in large hepatic wound, the results might be poor.

The use of protein solders to assist laser tissue welding has been reported previously (14). Concentrated albumin as a solder agent has been described in laser vascular anastomosis, urethroplasty, enterocystoplasty and various tissue closures (15). The laser tissue soldering relies upon covalent or noncovalent crosslinking of protein substrates induced by adding energy from lasers (14,15). The solder provides an appropriate strength and tolerance to the jointed tissues. In the previous study, we created a grade III to V hepatic injury model, which is similar to current model of ABC treatment. The preliminary works have demonstrated that using a 52% concentrated albumin solder with 810 nm diode laser we are able to fix the severe hepatic injuries with a free autologous omentum scaffold under Pringles' maneuver vascular control in the animal model (19). However, this technique requires expensive laser equipment and eye protection. Moreover, it requires incorporating ICG in the albumin. This combination creates issues with photostability of the dye during sterilization and storage. Our experimental experience also indicated that it was necessary to use an omental scaffold to enhance tolerance of the fused surface. Additionally, the spot size and energy power of the laser made the repair at least two times slower than using ABC.

Argon ion beam coagulator is a popular tool using for hemostasis in the surgical field. However, venous embolism is a concern (5) although it rarely occurrs. Our study has suggested that the concentrated albumin seals the wound surface of liver and may prevent argon gas from entering open vein and bile ducts. Our preliminary experiments indicated that a 38% albumin mixture assistance with ABC applied to a divided liver resulted in considerable bonding strength and more favorable application characteristics when compared to more or less concentrated solders (21). Our results demonstrated that ABCA is more effective in term of providing hemostasis of liver hemorrhage than ABC does. One animal died after surgery in the ABC group. A further investigation to this death explored a delayed bleeding

problem from repaired liver resection. In the ABCA group, one animal developed peritonitis and was sacrificed on the 4th day after surgery. Autopsy examination observed that intraperitoneal nodules developed diffusely along with abdominal cavity that could have been a secondary fungal infection, unfortunately that was not confirmed by pathogenic examination. The source of the infection remained unclear. Both cases were excluded in this study.

The present study showed that animals in both groups were healthy without system reaction and complications. Histopathology study presented there were similar acute and chronic local reactions at both groups. The benign inflammatory response could be a long term healing process that depends on a size of repairs, the amount of albumin used, and host immunosensitivity to the coagulated albumin. Furthermore, there were no system toxicity and local cytotoxicity presented at the repaired livers.

CONCLUSIONS

The study demonstrated that the argon beam coagulation associated with the concentrated albumin is a safe, quick and reliable hemostasis technique, and may be used in patient who presents coagulation failure. Use of this technique could potentially reduce morbidity and mortality complicated with solid visceral organ trauma. This technique can be transferred for using other energy sources and also be suitable for various endoscopic or laparoscopic applications.

ACKNOWLEDGMENTS

REFFERENCES

1. Suuerburch T, Wotzka R. Heilmann KL, Gorisch W, Kaess H: Thermal coagulation of puncture lesions in the cholestatic rabbit liver with Nd:YAG laser and an high-frequency current. Hepatogastroenterology. 1980 Jun; 27(3): 195-9
2. Carmona RH, Peck DZ, Lim RC: The role of packing and planned reoperation in severe hepatic trauma. J. Trauma 1984; 24(9): 117-24
3. Shimanuki T, Nishimura k, Montz FJ, Nakamuura RM, diZerega GS: Localized prevention of postsurgical adhesion formation and reformation with oxidized regenerated cellulose. J Biom Mat Res. 1987; 21: 173-85
4. Beal, SL: Fatal hepatic hemorrhage: An unresolved problem in the management of complex liver injury. J Trauma. 1990; 30; 163-9
5. ECRI Evaluation: Argon beam coagulation systems. Health Devices 1990 Sep; 19(9): 299-320
6. Dowling RD, Ochoa J, Yousem SA, Peitzman A and Udekwu AO: Argon beam coagulation is superior to conventional techniques in repair of experimental spleenic injury. J Trauma 1991; 31 (5):717-21
7. Berguer R, Staetrkel RL, Moore EE, Moore FA, Galloway WB, Mockus MB: Warning: fatal reaction to the use of fibrin glue in deep hepatic wounds. Case report. J Trauma 1991 Mar; 31(3): 408-11
8. Go PM, Goodman GR, Bruhn EW, Hunter JG: The argon beam coagulator provides rapid hemostasis of experimental hepatic and splenic hemorrhage in anticoagulated dogs. J Trauma 1991 Sep;31(9):1294-300
9. Kohno H, Nagasue N, Chang YC, Taniura H, Yamanoi A, Nakamura T: Comparison of topical hemostatic agents in elective hepatic resection: a clinical prospective randomized trial. World J Surg. 1992 Sep-Oct; 16(5): 966-70
10. Postema RR, Plaisier PW, ten Kate FJ, Terpstra OT: Haemostasis after partial hepatectomy using argon beam coagulation. Br J Surg 1993 Dec;80(12):1563-5
11. ECRI: Fatal gas embolism caused by overpressurization during laparoscopic use of argon enhanced coagulation. Health Device 1994 Jun; 23(6):257-9
12. Kitamura K, Yasuoka R, Ohara M, Shimotsum M, Hagiwara A, Yamane T, Yamaguhi T, Takahashi T: How safe are the xenogeneic hemostats? Report of a case of severe systemic allergic reaction. Surg Today 1995; 25(5): 433-5

13. Kato T, Suto Y, Hamazoe R: Effects of microwave tissue coagulation on the livers of normal rabbits: a comparison of finding of image analysis and histopathological examination. Br. J Radiol. 1996 Jun; 69 (822): 515-21
14. Kirsch AJ: Laser tissue soldering: State of the art. Contemporary Urol. 1997; 41-60
15. Scherr DS Poppas DP: Laser Tissue Welding. Urol. Clin. Nor Am. 1998; 25(1): 123-135
16. Stojeba N, Mahoudeau G, Segura P, Meyer C, Steib A: Possible venous argon gas embolism complicating argon gas enhanced coagulation during liver surgery. Acta Anaesthesiol Scand 1999 Sep;43(8):866-7
17. Wood TF, Rose DM, Allegra DP, Foshag LJ, Bilchik AJ: Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. Ann Surg Oncol. 2000 Sep; 7(8); 593-600
18. Vaezy S, Martin R, Crum L: High intensity focused ultrasound: a method of hemostasis. Echocardiography. 2001 May; 18(4): 51-9
19. Wadia Y, Xie H, Kajitani M: Sutureless liver repair and hemorrhage control using laser-mediated fusion of human albumin as a solder. J trauma 2001 Jul; 51(1):51-9
20. Wolf RF, Xie H, Petty J, Teach JS, Prahl SA: Argon Ion Beam Hemostasis with albumin following live resection. Am J Surg (Submitted)
21. Moffitt TP, Baker DA, Kirkpatrick SJ, Prahl SA: Mechanical properties of coagulated albumin and failure mechanism of liver repaired using argon beam coagulator with albumin. J Biom Mat. Res. (Submitted)

[a]Contact authors: Hua Xie, MD, PhD; hxie@providence.org; phone:1-503-216-6826; fax: 1-503-216-5256; Scott Prahl, PhD; prahl@ece.ogi.edu; phone: 1-503-216-2197; 9205 SW Barnes Rd, Portland, OR 97225

Figure 1. Liver resection repaired using an albumin with the ABC (ABCA). A layer of coagulated albumin coated on the raw surface of liver resection.

Figure 2. Liver resection was repaired using the ABC alone. A layer of carbonated tissue coated on the raw surface.

Figure 3. ABCA repaired liver at 3 months. The liver repaired surface adhered to abdominal cavity. No adhesion was noted in surrounding organs.
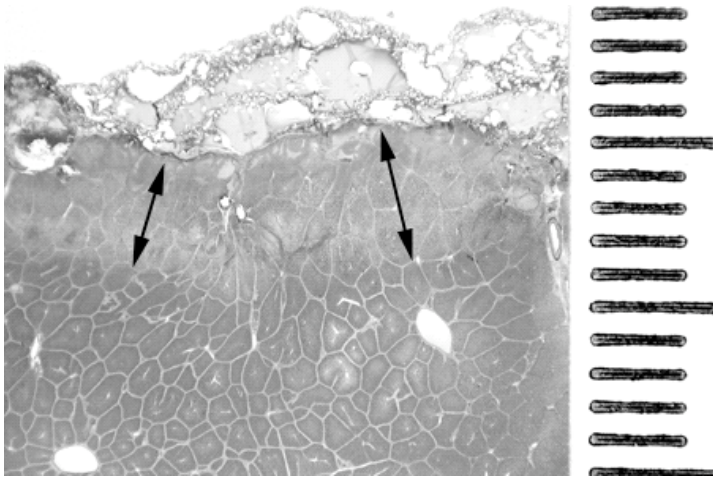
Figure 4. A cross section shows the surface coagulation necrosis (black arrows) and underlying area of hyperemia at acute reaction after ABC alone. Note the cauterized plasma and tissue on the treatment surface. (Movat stain, 25X)
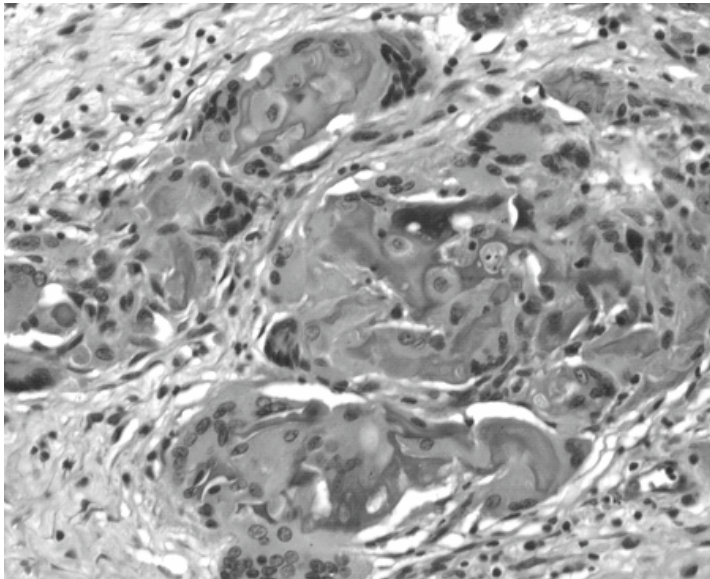

Figure 5. A cross-section of liver repair shows numerous giant cells with engulfed albumin and surrounding granulation tissue at 1 month after ABC alone (H & E stain, 400X)
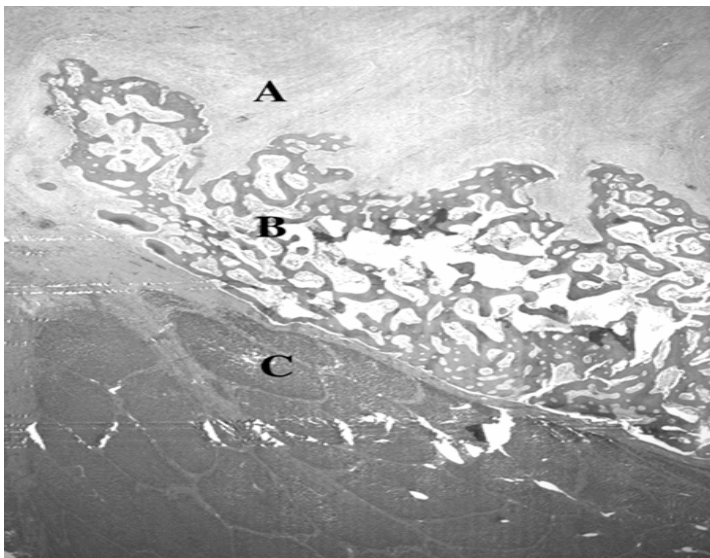

Figure 6. A cross section of liver repair after 3 months. It shows the granulation tissure (A), ossified area (B), and the liver parenchyma with perilobular fibrosis adjacent to the treatment site (C). (Movat stain, 50 X)
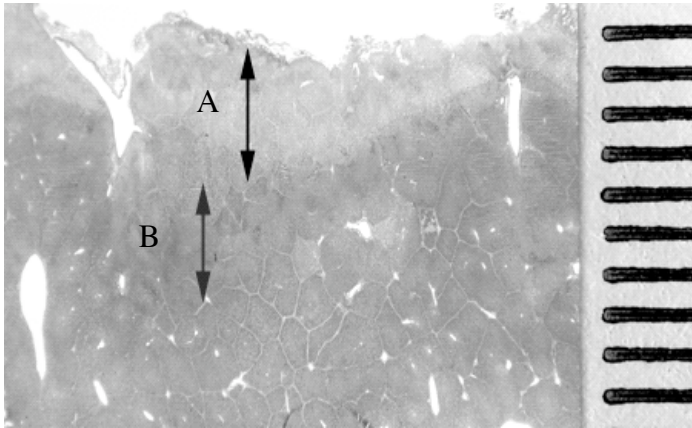
Figure 7. A cross section of liver repair shows the surface coagulation necrosis (arrow A) and underlying area of hyperemia (arrow B) at acute reaction after ABCA. (Movat stain, 25 X)
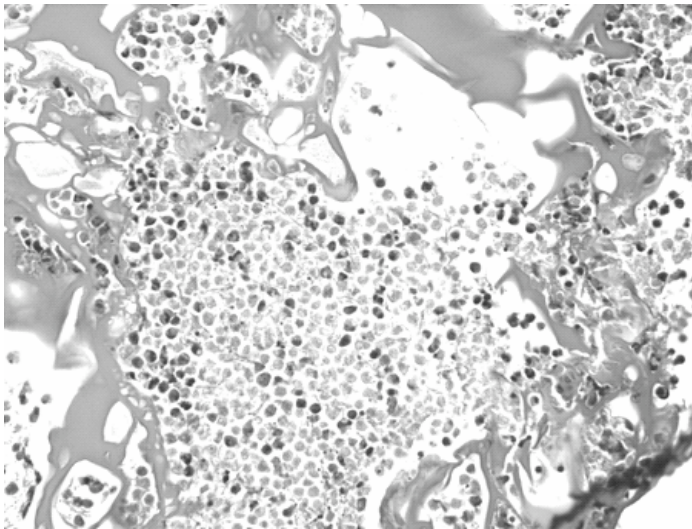

Figure 8. A cross section of the center of an abscess cavity with albumin, necrotic inflammatory reaction with lymphocytes, eosinophils, macrophages infiltration at 1 month after ABCA. (H&E stain,100X).

Figure 9. A cross section showing a chronic inflammatory response with giant cell reaction (1), bone formation (2), fibrous reaction with rich proteoglycan present (3), and layer of elastin membrane (4)
at 3 months after ABCA. (Movat stain, 50X)