DR. BRIAN DAVIS (Orcid ID : 0000-0002-7567-6748)

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bcd2013@gmail.com

Heat Stroke Leading to Acute Liver Injury & Failure: A Case Series from the Acute Liver Failure Study Group

Brian C. Davis,* Holly Tillman,‡ Raymond T. Chung,§ R. Todd Stravitz,# K. Rajender Reddy,¶ Robert J. Fontana,^ Brendan McGuire,% Timothy Davern,& William M. Lee* for the Acute Liver Failure Study Group

Author Affiliations:

*Division of Digestive and Liver Diseases, UT Southwestern Medical Center, Dallas, TX; ‡Department of Public Health Sciences, Medical University of South Carolina,

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Charleston, SC; [§]Department of Gastroenterology, Massachusetts General Hospital, Boston, MA; [#]Division of Gastroenterology, VCU Medical Center, Richmond, VA; [¶]Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ^Division of Gastroenterology, University of Michigan Health System, Ann Arbor, MI, [%]Division of Gastroenterology and Hepatology, UAB School of Medicine, Birmingham, AL, [&]California Pacific Medical Center, San Francisco, CA.

Author Contributions:

Study Design: B.C. Davis and W.M. Lee
Analysis and Interpretation of Data: B.C. Davis, H. Tillman, W.M. Lee
Drafting of the Article: B.C. Davis
Critical Revisions of the Article: B.C. Davis, R.T. Chung, R.T. Stravitz, K.R. Reddy, R.J. Fontana. B. McGuire, W.M. Lee
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Obtaining of Funding: W. M. Lee
Collection and Assembly of Data: B.C. Davis, H. Tillman, R.T. Chung, R.T. Stravitz, K.R. Reddy, R.J. Fontana B. McGuire, T. Davern, W.M. Lee

Correspond with:

William M. Lee, MD, FACP, FAASLD
Division of Digestive and Liver Diseases
UT Southwestern Medical Center at Dallas
5959 Harry Hines Blvd. Ste 420
Dallas, TX 75390-8887

Key Points

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- Heat stroke is a rare cause of acute liver injury and failure
- Majority of patients were young, previously healthy males and developed exertional heat stroke
- Clinical features included acute kidney injury, lactic acidosis, thrombocytopenia and rhabdomyolysis
- Supportive care with cooling protocols led to transplant free survival in 5 of 8 patients

Abbreviations:
ALI: acute liver injury; ALF: acute liver failure; NAC: *N*-acetyl-cysteine; CHS: classical heat stroke; EHS: exertional heat stroke; LT: liver transplantation; ALFSG: Acute Liver Failure Study Group; INR: international normalized ratio; HE: hepatic encephalopathy, TFS: transplant free survival; IQR: interquartile range; ED: emergency department: ALT; alanine aminotransferase; AST: aspartate aminotransferase; AKI: acute kidney injury; sCR: serum creatinine; ICU: intensive care unit; RRT: renal replacement therapy; HVP: high volume plasma exchange

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Abstract:

Objective: In the United States, nearly 1000 annual cases of heat stroke are reported but the frequency and outcome of severe liver injury in such patients is not well described. The aim of this study was to describe cases of acute liver injury (ALI) or failure (ALF) caused by heat stroke in a large ALF registry. *Data Sources:* Amongst 2,675 consecutive subjects enrolled in a prospective observational cohort of patients with ALI or ALF between January 1998 and April 2015, there were 8 subjects with heat

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stroke. *Data Synthesis:* Five patients had ALF and 3 had ALI. Seven patients developed acute kidney injury, all 8 had lactic acidosis and rhabdomyolysis. Six patients underwent cooling treatments, 3 received *N*-acetyl cysteine (NAC), 3 required mechanical ventilation, 3 required renal replacement therapy, 2 received vasopressors, 1 underwent liver transplantation, and 2 patients died—both within 48 hours of presentation. All cases occurred between May and August, mainly in healthy young men due to excessive exertion. *Conclusions:* Management of ALI and ALF secondary to heat stroke should focus on cooling protocols and supportive care, with consideration of liver transplantation in refractory patients.

Key Words

Heat stroke, acute liver failure, multi organ system failure, liver transplantation, rhabdomyolysis

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Introduction:

There were an estimated 7,233 heat-related deaths in the United States from 1999-2009.[1] The most serious heat-related illness is heat stroke,[2] defined as having elevated body temperature ≥ 40°C with central nervous system dysfunction, and is divided into classical and exertional sub-types. Classical, or non-exertional, heat stroke (CHS) is more common in elderly and immunocompromised individuals and associated with elevated environmental temperatures such as in heat waves. Exertional heat stroke (EHS) occurs in younger individuals associated with vigorous activities such as marathons.[3,4] Over the next century, the frequency and intensity of heat waves will likely increase due to climate change.[5] Heat stroke should be preventable and early diagnosis and treatment could reduce morbidity and mortality.

Hepatocellular injury is a well-documented complication of heat stroke,[6] but few case reports[7-9] have described an association with acute liver injury or failure (ALI/ALF). Treatment of ALF from heat stroke involves mainly supportive care;[8] few centers have performed liver transplantation (LT).[10,11] We describe the clinical characteristics and

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outcomes of ALI and ALF caused by heat stroke in a large North American prospective ALI/ALF cohort.

Methods

Between January 1998 and April 2015, 2,675 adult patients with ALI or ALF of all etiologies were enrolled in the Acute Liver Failure Study Group (ALFSG) registry from a total of 31 academic medical centers in North America. All patients enrolled met entry criteria for ALF, defined as coagulopathy (INR ≥ 1.5), and any grade of hepatic encephalopathy (HE defined clinically by the West Haven criteria[12]), within 26 weeks of the first symptoms and in the absence of pre-existing chronic liver disease.[13] A second category of patients were classified as acute liver injury (ALI), which has been defined by the ALFSG as patients with an INR ≥ 2.0 in the absence of preexisting liver disease and no encephalopathy. The overall study design and human research concerns were reviewed every 6 months by a Data and Safety Monitoring Board appointed by the National Institute of Digestive and Kidney Diseases (NIDDK). In addition, each center's Institutional Review Board approved the study on an annual basis. Informed consent was obtained directly from ALI patients. In cases meeting criteria for ALF, consent was obtained from each patient's next of kin or health proxy, since by definition patients were unable to consent due to encephalopathy, and consent was revisited with the patient following recovery of mental functioning (Supplemental Forms 1 and 2). Clinical data and bio-samples were collected from each study subject for 7 days with follow up visits at 6 months and 1 year. The ALF etiology was determined by the site investigator and later reviewed by a central causality committee for confirmation. Eight cases were classified by the site investigator as "Other: heat stroke" and subsequently confirmed by temperature ≥ 40°C and clinical data to rule out other causes. If the patient's encephalopathy resolved after resuscitation for heat stroke and the INR was ≥ 2.0, the patient was diagnosed with ALI. If the encephalopathy persisted after resuscitation for heat stroke, the patient was diagnosed with ALF.

Each site utilized its own criteria for liver transplantation but in general followed AASLD guidelines and the United Network Organ Sharing (UNOS) Status 1 criteria: age ≥18 years, life expectancy <7 days without liver transplantation, residence in an

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intensive care unit (ICU), no pre-existing liver disease, and either ventilator dependence, renal replacement therapy, or INR >2.0.[13,14] Descriptive analysis was used to compare patient demographics, medical history, clinical characteristics, and outcomes (transplant-free survival [TFS], LT, death). We also compared ALI/ALF heat stroke patients to acetaminophen (APAP) and ischemia etiologies of ALI/ALF. Medians were reported with interquartile ranges (IQR) and compared with the Wilcoxon rank-sum test. Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Clinical Presentation

Five of the 8 patients had ALF and 3 had ALI. There were 7 patients with EHS and one with CHS. Four EHS cases were associated with long distance running, one was associated with treadmill use while wearing a sweat suit and wrapped in plastic, one was associated with military drills, and one was found unconscious in a field. The CHS case occurred in an individual who lived alone and was found unresponsive in his apartment. All cases occurred between May and August. Seven patients were male, and the median age was 31 years (range 22-45 years). All patients were previously healthy without medical co-morbidities. The median temperature at presentation was 40.7℃ (IQR 40.6-42.2℃). Two patients entered the ALFSG registry without documented temperatures >40℃, but were later classified as heat stroke by the site investigator after other ALF causes were ruled out. All patients tested negative on a urine drug toxicology screen. Grade 3 or 4 hepatic encephalopathy was present in 80% of patients with ALF. Five patients initially presented to an outside emergency department (ED) and were transferred to an ALFSG study site for higher level of care (median time to transfer 2.5 days [range 1-8 days]).

Laboratory Values on Admission

Three patients had normal liver enzymes at ED presentation prior to study enrollment. Liver injury was very severe in all cases, with a mixed hepatocellular and cholestatic pattern. Seven of eight patients developed acute kidney injury, and all 8 had lactic acidosis and rhabdomyolysis. When compared with ALI or ALF patients from APAP or ischemia, patients with heat stroke were younger, mostly male, and had similar

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blood pressure on admission but had more severe liver injury, thrombocytopenia, and elevated serum creatinine, lactate, and creatine kinase (Table 1). Ammonia levels were recorded in 6 patients on admission (median 50.5 μmol/L [IQR 29-70.5 μmol/L) with the maximum value being 130 μmol/L in a patient with spontaneous survival.

Management

Six patients underwent documented cooling protocols. All patients were admitted to the intensive care unit (ICU) at the study site. Each patient achieved normothermia, defined as temperature <38℃, within 24 hours of study enrollment. The majority of patients had stable hemodynamics throughout admission, but 2 patients required vasopressors. Three patients required mechanical ventilation, 3 received N-acetyl cysteine (NAC), 3 underwent renal replacement therapy (RRT), one had an intracranial pressure monitor (ICP) placed, and none received mannitol.

Outcomes

Five patients recovered with supportive care alone, although one had been initially listed for LT. One patient underwent combined kidney/liver transplantation due to persistent anuric renal injury requiring 3 weeks of RRT and was alive at one year of follow up. Two patients died—both within 48 hours of admission from multi-organ system failure. In the first case, the patient was attempting to lose weight by taking dietary supplements, diuretics, and running on a treadmill wearing a sweat suit wrapped in plastic. His initial temperature was 42.2℃ and was cooled but had a rapidly deteriorating clinical course requiring mechanical ventilation, vasopressors, and RRT. The second patient found unconscious in his apartment with a temperature of 42.2℃. He underwent cooling but required vasopressors, mechanical ventilation, RRT, and ICP monitor placement for persistently impaired mental status, which showed normal measurements. He was not deemed a candidate for LT. Histopathology of the CHS case at autopsy demonstrated massive hepatocellular necrosis, with centrilobular hemorrhage (Figure 1).

Overall, the median length of stay in the series was 5 days (IQR 2.75-38.25 days). No long-term sequelae were observed in survivors at one year of follow up and all laboratory abnormalities returned to normal.

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Discussion

Our series demonstrates that heat stroke is a rare cause of ALF. All but one of our cases occurred in young, previously healthy males enduring excessive exertion during summer months. Most cases occurred outdoors after long distance running, with distances ranging from 5-20 kilometers. While TFS was the most frequent outcome, ALF from heat stroke can be fatal, and both deaths were attributed to multi-organ system failure. Factors that portend a poor prognostic outcome included temperature >42℃, rapid multi-organ failure requiring artificial organ support, and circulatory collapse requiring vasopressors.

In our series, management of heat stroke and ALF focused on supportive care with one case undergoing successful liver transplantation. Initial treatment should concentrate on cooling protocols, with the goal of achieving normothermia within 6 hours. While specific cooling protocols were not documented in these cases, as patients were enrolled in the ALFSG registry after ED resuscitation, previous studies on EHS patients indicate the best method for cooling involves immediate cold water immersion at very cold temperatures (1-14℃) or ice water.[15] Hepatocellular injury may be delayed by up to 24 hours, as several patients in our series had normal chemistries on presentation. In patients who develop worsening coagulopathy or encephalopathy, transfer to centers with expertise in organ transplantation should be considered.

It is important for the clinician to maintain a high index of suspicion for ALI or ALF in a patient with heat stroke as the diagnosis of ALF and heat stroke overlap with respect to altered mental status. For instance, a patient's persistent encephalopathy after heat stroke may be the first clinical sign of acute liver failure.

All patients with heat stroke and ALI/ALF should be admitted to an ICU for close monitoring, as supportive care of ALF patients in the ICU has improved TFS and overall survival over the past decade.[16]

The mechanisms that lead to multi-organ failure in heat stroke remain unclear, but studies suggest the systemic inflammatory response (SIRS) plays a critical role in cellular injury after heat exposure by activating pathways leading to cellular necrosis and apoptosis.[17] Heat stroke has been shown to induce liver injury in rats via the

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interlukin-1B pathway.[18] The tissues most sensitive to changes in temperature are brain and liver, but heat also damages kidney, myocardium, muscle, and the gastrointestinal tract. Ischemic hepatitis may also develop related to vascular collapse from dehydration and shunting of blood from the splanchnic circulation to the skin in order to dissipate heat.[2] Thrombocytopenia, as seen in all our patients, is associated with SIRS activation and poor prognosis in ALF patients.[19]

Future therapies designed to target the inflammasome, such as high-volume plasma exchange (HVP), could be promising in patients with heat stroke and ALF. HVP was successful in a single individual who develop CHS and ALF after prolonged sauna exposure[20] and improved TFS in an open-label randomized trial of 182 ALF patients.[21]

Conclusions

Heat stroke is a rare, but severe and potentially fatal cause of ALF—frequently due to over-exertion by young males in early summer months. Prompt recognition and measures to prevent such occurrences should be stressed to medical providers and public health officials.

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Figure Legend

Figure 1. Autopsy histopathology of the liver in a patient who died from heat stroke and acute liver failure: (A) massive hepatocyte necrosis throughout nearly the entire lobule, x40; (B, C) Showing viable bile duct in portal tract, rare viable hepatocytes in periportal zone, hemorrhagic necrosis in centrilobular zone, picture B at x100, C at x200. Autopsy was performed within 6 hours of death.

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ALI/ALF Etiology	Heat Stroke (n=8)		APAP (n=1289)		Ischemia (n=152)	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Baseline characteristics						
Age (year)	8	31.0 (25.5-35.5)	1289	36.0 (27.0-46.0)	152	53.0 (39.0-60.0)
Sex (%)	8	Male (87.5)	1289	Male (25.8)	152	Male (44.1)
Race (%)	8	White (100.0)	1289	White (85.0)	152	White (77.6)
Maximum Temp (°C)	8	40.7 (40.6-42.2)	1262	37.1 (36.7-37.6)	148	36.9 (36.5-37.4)
MAP	8	90.8 (85.0-93.3)	1282	87.7 (76.3-98.7)	152	86.8 (73.0-99.0)
Laboratory Values on Admission						
Platelet (10^3/μL)	8	45.5 (35.5-67.5)	1270	129.0 (88.0-185.0)	151	88.0 (55.0-129.0)
INR	8	3.5 (2.9-4.3)	1258	2.8 (2.0-4.3)	150	2.4 (1.9-3.2)
AST (IU/L)	8	5179.0 (1784.5-9897.5)	1279	3963.0 (1599.0-7821.0)	152	2570.5 (1061.5-5850.0)
ALT (IU/L)	8	6092.0 (3882.5-8811.5)	1278	3993.0 (2087.0-6537.0)	151	2178.0 (1288.0-4260.0)
ALP (U/L)	8	109.5 (82.0-137.0)	1258	115.0 (88.0-154.0)	148	36.9 (36.5-37.4)
Total Bilirubin (mg/dL)	8	8.8 (5.8-10.7)	1274	4.1 (2.4-6.1)	151	3.8 (2.2-6.6)
sCr (mg/dL)	8	2.4 (1.4-6.0)	1284	1.5 (0.8-3.0)	152	2.4 (1.4-3.7)
CK (U/L)	8	3662.0 (2501.0-41250.0)	385	365.0 (149.0-1425.0)	83	578.0 (141.0-2506.0)
Lactate (mg/dL)	8	6.7 (5.6-12.4)	757	3.8 (2.2-8.2)	104	3.7 (2.4-7.1)
Peak Values During Admission						
INR	8	4.2 (3.0-4.6)	1276	3.0 (2.1-4.7)	151	2.5 (1.9-3.6)
AST (IU/L)	8	5179.0 (1784.0-9897.5)	1287	4500.0 (1900.0-8500.0)	152	2764.0 (1083.5-6016.0)
ALT (IU/L)	8	6092.0 (4259.0-8811.5)	1285	4400.0 (2426.0-6970.0)	152	2257.5 (1326.5-4316.5)
ALP (U/L)	8	123.0 (99.0-198.5)	1264	126.0 (94.0-168.0)	148	141.5 (102.0-227.5)
Total Bilirubin (mg/dL)	8	12.9 (11.0-25.9)	1284	6.2 (3.4-10.7)	152	5.6 (2.8-12.2)
sCr (mg/dL)	8	4.3 (1.4-6.4)	1287	1.9 (0.9-4.4)	152	2.7 (1.6-4.9)
CK (U/L)	8	12346.0 (2626.0-48770.0)	420	373.0 (150.5-1431.5)	93	607.0 (129.0-2753.0)
Lactate (mg/dL)	8	8.8 (6.7-13.1)	842	3.9 (2.2-8.6)	112	3.8 (2.5-7.8)

Table 1. Comparison of patients presenting with acute liver injury or failure (ALI/ALF) secondary to heat stroke, APAP, or ischemia. Baseline values are compared with laboratory values on admission and peak values during study enrollment. Abbreviations: ALP, alkaline phosphatase; ALT, alanine

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aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; CK, creatine kinase; INR, international normalized ratio; MAP, mean arterial pressure; sCR, serum creatinine.

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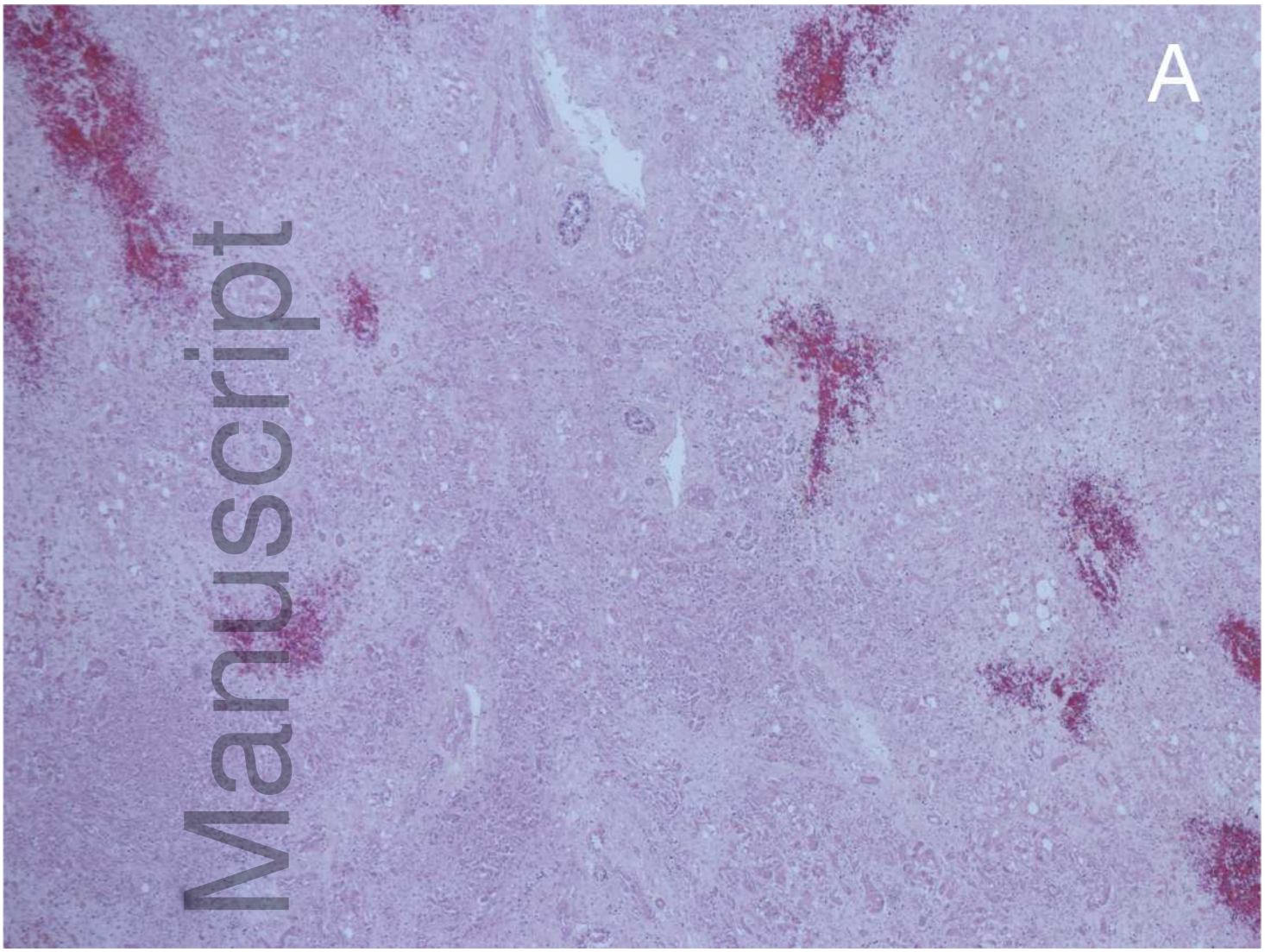

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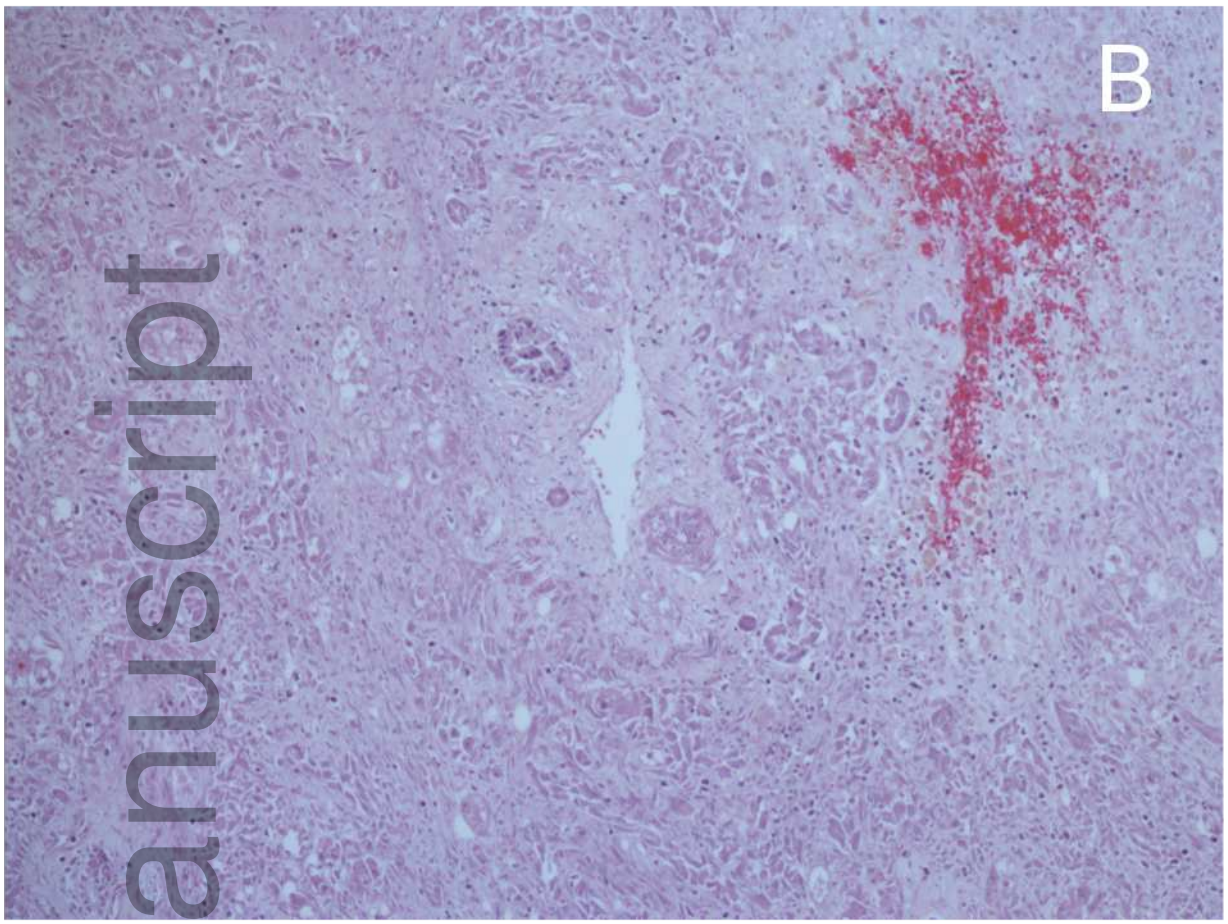

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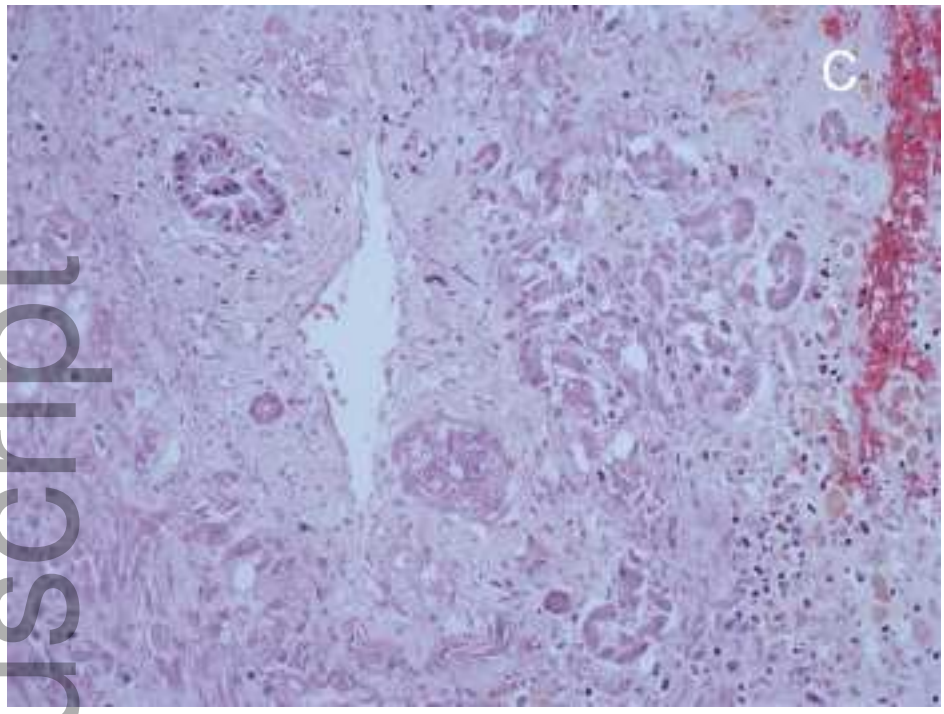

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