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# Pancreaticoduodenal Arterial Rupture and Hemoabdomen in ACI/SegHsd Rats with Polyarteritis Nodosa

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**Many lesions associated with aging have been well-characterized in various strains of rats. Although documented in Sprague–Dawley and spontaneously hypertensive rats, polyarteritis nodosa has not previously been reported in ACI/SegHsd rats. ACI/SegHsd rats were maintained on high-fat (40.5%), low-fat (11.6%), and high-fat to low-fat dietary protocols to examine the correlation between dietary fat and the regulation of prostate 5α-reductase gene expression and prostate cancer. Seven rats died unexpectedly with hemoabdomen and rupture of the pancreaticoduodenal artery secondary to polyarteritis nodosa (PAN). The purpose of this study was to analyze the pathologic findings in these and the remaining ACI/SegHsd rats and to correlate the level of dietary fat with the presence of PAN, arterial rupture, and hemoabdomen. Approximately 65% of the rats had evidence of PAN by histopathology, with a 24% incidence of arterial rupture. Additional lesions noted included an 88% incidence of chronic progressive nephropathy (CPN) and a 32% incidence of cartilaginous foci in the aortic valve. We found no association between the percentage of dietary fat and incidence of PAN, CPN, or cardiac cartilage. Although arterial rupture is a known complication of polyarteritis nodosa in humans, this case series is the first to document arterial rupture and hemoabdomen in rats with PAN.**

**Abbreviations:** CPN, chronic progressive nephropathy; HF, high-fat; HL, high- to low-fat; LF, low-fat; PAN, polyarteritis nodosa; SHR, spontaneously hypertensive rat

Polyarteritis nodosa (PAN) is a multicentric vasculitis of small- to medium-sized arteries. The etiology of PAN in humans is postulated to be immune-mediated via immune complex deposition associated with numerous inciting factors, such as viruses (hepatitis B and C) and drug reactions, or idiopathic in nature.[8,21,31] PAN has been previously reported in laboratory rats in experimentally manipulated animals or as a spontaneous disease in certain strains. Sprague–Dawley rats have the highest reported incidence of PAN among outbred strains.[27] In the only published large-scale study documenting the incidence of PAN in Sprague–Dawley rats,[43] experimentally manipulated aged male and female rats demonstrated a 14.6% incidence of the syndrome, but treated and untreated animals did not differ significantly. The inbred strain most commonly associated with PAN is the spontaneously hypertensive rat (SHR), including both the stroke-prone and stroke-resistant variants. A 100% incidence of PAN in the testicular arterioles and 60% incidence in the mesenteric arteries were documented in a group of aged (15.5 mo) stroke-prone SHR rats.[29] The cited study also documented PAN in aged stroke-resistant rats, with a slightly lower incidence than that of the stroke-prone animals (42.9% testicular and 28.6% mesenteric). Other affected strains that have been reported include Holtzman and red-hooded rats, with lesions primarily in aged females.[7] To our knowledge, PAN in ACI/SegHsd (August Copenhagen Irish) rats has not been reported previously.

The ACI/SegHsd inbred rat strain was developed in 1926 at the Columbia University Institute for Cancer Research. The median lifespan of this strain is approximately 27.5 mo. These animals have a high incidence of spontaneous prostatic adenocarcinomas[25] and a high-fat diet increases the incidence of these tumors, thus making this strain a good model for prostate cancer research. Congenital renal lesions have been documented extensively among ACI/SegHsd rats and include renal agenesis and hypoplasia,[13] with incidences of approximately 12% in males and 14% in females for both abnormalities.[5] Although less frequent than renal agenesis, hydronephrosis has been reported to occur in ACI/SegHsd rats.[13]

A group of aged, male ACI/SegHsd rats were on an experimental protocol in which they were fed diets that varied in fat content for 95 wk (or until the time of death) to examine the correlation between fat and the regulation of prostate 5α-reductase gene expression and prostate tumorigenesis.[6] The 3 diets included a high (40.5%)-fat diet, a low (11.6%)-fat diet, and a high-to-low fat diet. Eight animals presented with hemoabdomen (7 presented dead), with gross and histopathologic lesions of PAN and rupture of the pancreaticoduodenal artery. The purpose of the present study was to analyze the pathologic changes in these and the remaining ACI/SegHsd rats to correlate the presence of PAN, arterial rupture, and hemoabdomen with the level of fat in the diet. We also present a brief overview of PAN and related conditions in laboratory animals and humans.

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## Materials and Methods

**Animals and diet regimen.** Beginning at weaning (20 to 21 d), male ACI/SegHsd rats (Harlan Sprague Dawley, Indianapolis, IN) were fed either a low-fat (LF, 11.6 kcal %fat) or high-fat (HF, 40.5 kcal %fat) diet or were switched from a high- to a low-fat (HL) diet after 4 wk (Table 1). The scheduled endpoint of the study was 95 wk of dietary treatment. The diets were prepared by Research Diets (New Brunswick, NJ) and stored at 4 °C. Food and water were supplied ad libitum. Fresh food was replaced on a weekly basis. Animals came from colonies certified free of rat coronavirus–sialodacryoadenitis virus, Sendai virus, pneumonia virus of mice, rat parvovirus, Kilham rat virus, Toolan H1 virus, reovirus 3, lymphocytic choriomeningitis virus, Hantaan virus, Theiler murine encephalomyelitis virus (strain GDVII), *Mycoplasma pulmonis*, cilia-associated respiratory bacillus, *Bordatella bronchiseptica*, *Corynebacterium kutscheri*, *Pasteurella pneumotropica*, *Klebsiella* spp., *Salmonella* spp., *Streptococcus* spp., and *Staphylococcus* spp. as well as all ecto- and endoparasites. The animals were housed in plastic cages with woodchip bedding in the Research Animal Resource Center of Weill Medical College of Cornell University, which is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. The rats were maintained on a 12:12-h light:dark cycle (0600 to 1800) and cared for in accordance with the *Guide for the Care and Use of Laboratory Animals*[6] All experimental procedures received approval from the institutional animal care and use committee.

**Necropsy and histologic grading of PAN.** Rats died spontaneously or were euthanized by carbon dioxide asphyxiation; complete postmortem evaluations were performed on 34 rats. Representative samples from all tissues (excluding central nervous system and prostate) were examined. Tissues were fixed in 10% neutral buffered formalin, with the exception of the sternum and femur, which were fixed in Decalcifier I (Surgipath Medical Industries, Richmond, IL) for 48 h. All tissues were processed by routine methods and embedded in paraffin wax. Sections (5 µm) were stained with hematoxylin and eosin, and evaluated by light microscopy (Olympus BX45, New York/New Jersey Scientific, Middlebush, NJ). Select vascular lesions also were stained with Masson's trichrome for connective tissue and Verhoeff–Van Gieson for elastin fibers.All tissues were evaluated for evidence of PAN lesions, which were graded as follows: 0, no evidence of PAN; 1, subintimal to medial fibrinoid vascular necrosis or fibrosis (or both conditions) with infiltrating neutrophils, lymphocytes, or plasma cells (or any combination of these cell types) affecting a single arteriole or artery ; 2, multiple arterioles or arteries (or both types of vessels) affected in a single tissue or multiple tissues; and 3, multiple arterioles or arteries (or both types of vessels) with evidence of thrombosis, aneurysmal dilatation, dissection, or rupture (or any combination of these abnormalities).

**Statistical analysis.** Simple Interactive Statistical Analysis[41] was used to perform Fisher exact tests to evaluate the associations between diet (HF, LF, or HL) and identified lesions and between PAN lesions and age (analyzed for 3 age groups: 14 to 20, 21 to 27, and 28 to 34 mo). Chi-squared analysis (Minitab version 12.1, Minitab, State College, PA) was used to evaluate the association between the presence of PAN and chronic progressive nephropathy and cardiac cartilage. Statistical significance was indicated by a $P$ value of less than 0.05.

**Table 1.** Composition of experimental diets

| | High-fat diet (40.5 kcal %fat) gm | Low-fat diet (11.6 kcal %fat) gm |
|---|---|---|
| Casein | 200 | 200 |
| Corn starch | 100 | 100 |
| DL methionine | 3 | 3 |
| Cellulose | 50 | 50 |
| Maltodextrin-10 | 50 | 50 |
| AIN-76A vitamin mix[4] | 10 | 10 |
| AIN-76A salt mix[4] | 35 | 35 |
| Choline bitartrate | 2 | 2 |
| Sucrose | 219 | 500 |
| Corn oil | 175 | 50 |
| Total | 844 | 1000 |
| Energy (kcal/g) | 4.61 | 3.89 |

## Results

Ten animals (4 HF, 3 LF, 3 HL) died unexpectedly 56 to 91 wk after dietary treatment; 24 additional animals were necropsied at the scheduled endpoint of the experiment. A total of 34 rats (11 HF, 12 LF, and 11 HL) ranging from approximately 14 to 34 mo in age were examined. PAN lesions (score, 1 or greater) were present in 65% (22 of 34) of all rats (Table 2) and were restricted to 3 tissues: pancreas, testes or spermatic cord (or both tissues), and mesentery (Figure 1). The testes and spermatic cord had the greatest distribution of lesions, whereas the most severe lesions were present in the pancreas. Histologically, acute PAN lesions were characterized by prominence of vessels with normal mural architecture obscured by eosinophilic, fibrillar material and infiltrating, often degenerate neutrophils in subintimal to medial locations (Figure 2 C). With continued damage to the vascular wall, integrity of elastin fibers was lost (data not shown) as lymphocytes, plasma cells, and fibroblasts infiltrated the media (Figure 2 D). With chronicity, marked mural thickening resulted in narrowing of the vascular lumen (Figure 2 E). Aneurysmal dilatation, particularly of the cranial pancreaticoduodenal artery, often was present grossly in rats with and without evidence of rupture (Figure 2 B). Dissecting aneurysms evidenced by intramural hemorrhage (Figure 2 C) and hemosiderophages (Figure 2 F) were frequent in grade 3 PAN lesions. In addition, 36% (8 of 22) of rats with PAN (24% of the rats overall) had rupture of the pancreaticoduodenal artery and hemoabdomen. In these rats, variably sized hematomas were found in the left cranial abdomen, just caudal to the stomach overlying the pancreas (Figure 2 A).

There was no significant association between diet and the presence of grade 1 PAN or greater (Fisher exact test, $P = 0.37$), grade 2 PAN or greater (Fisher exact test, $P = 0.12$), or arterial rupture (Fisher exact test, $P = 0.21$). In addition, the presence of PAN lesions and age (14 and 34 mo) were not associated in our rats (Fisher exact test, $P = 0.11$).

Additional lesions frequently identified included chronic progressive nephropathy (CPN; 33 of 34 rats, 99%) and the presence of a cartilaginous focus in the aortic valve (11 of 34 rats, 32%). CPN was present in both kidneys of each affected animal. In 5 of the 34 rats, the heart was sectioned transversely through the ventricles; we thus were unable to rule out the presence of valvular cartilage in these animals. Further, 9 of the 11 animals with valvu-

**Table 2.** Pathologic changes in ACI/SegHsd Rats according to diet

| Diet | No. of rats | PAN ≥2 | PAN ≥1 | Rupture | CPN ≥1 | Valvular cartilage |
|---|---|---|---|---|---|---|
| HF | 11 | 4 | 9 | 4 | 11 | 3 |
| LF | 12 | 1 | 7 | 1 | 11 | 4 |
| HL | 11 | 5 | 6 | 3 | 11 | 4 |
| Total | 34 | 10 | 22 | 8 | 33 | 11 |
| Total Percentage | | 29% | 65% | 24% | 97% | 32% |

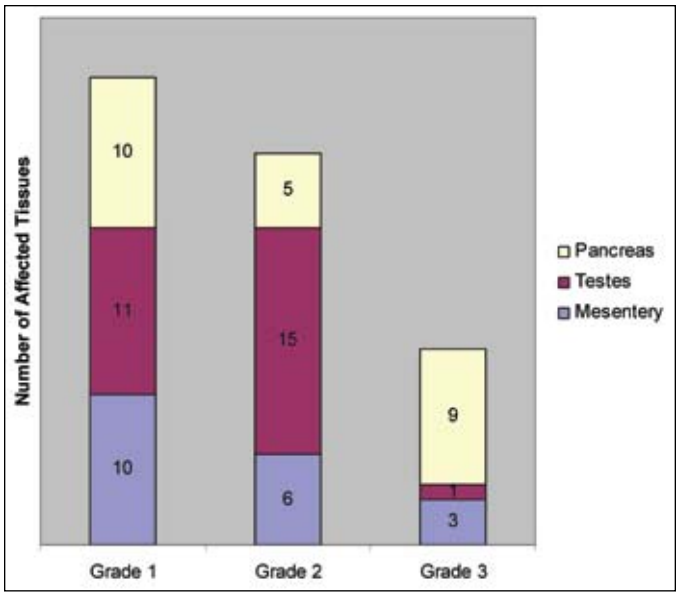


**Figure 1.** Grade and tissue distribution of PAN in ACI/SegHsd rats.

lar cartilaginous foci had a PAN score of 1 or greater. There was no significant association between diet and the presence of CPN or cardiac cartilage (Fischer exact test, $P = 0.81$), between the presence of PAN and CPN ($\chi^2 = 1.89$, df = 1, $P = 0.17$), or between PAN and the presence of cardiac cartilage ($\chi^2 = 0.036$, df = 1, $P = 0.85$).

Other common aging lesions noted in fewer animals included myocardial mineralization (6 of 34 rats), testicular atrophy (9 of 34 rats), unilateral or bilateral interstitial cell testicular tumors (5 of 34 rats), myocardial fibrosis (3 of 34 rats), adrenal adenomas (2 of 34 rats), mammary fibroadenoma (1 of 34 rats), renal adenoma (1 of 34 rats), and sublingual abscess (1 of 34 rats).

## Discussion

A total of 65% of the rats had histologic evidence of PAN at the time of presentation at necropsy, and 36% of these animals presented with acute pancreaticoduodenal arterial rupture. There was no association between the presence of PAN lesions and the level of dietary fat. PAN lesions have been reported mainly to occur in arteries of the mesentery, pancreas,[43] and testes[39] but have also been noted in other medium to large vessels, including hepatic, uterine, ovarian, adrenal, and cerebral arteries.[7] In SHR rats, most of the affected vessels were testicular arterioles, whereas mesenteric arteries had a lower overall incidence but more severe pathology.[29] The majority of lesions previously noted in Sprague–Dawley rats with PAN were located in the mesentery and pancreas but not testes.[43] The distribution and severity of lesions we noted in the current study reflected the findings previously reported for SHR rats. We identified a greater number of lesions in the testicular and spermatic arterioles, but lesions were more severe in the pancreas and mesentery. Saito[29] thought these differences were a reflection of the differences in local perfusion pressure between the mesenteric and testicular arterioles.

The etiology of PAN in laboratory rats is not clear but has been associated with hypertension, estrogen treatment, corticosteroid administration, exposure to chemical carcinogens, and hypersensitivity or immune-mediated mechanisms.[7] Transgenic rats created by introducing the *env-pX* gene of human T-cell leukemia virus type-I into inbred Wistar–King–Aptekman–Hokudai rats were established to evaluate the pathogenic role of this gene.[44] These transgenic rats developed necrotizing vasculitis comparable to PAN. This model has subsequently been used to examine the role of the thymus in development of arteritis.[12] PAN has also been induced experimentally by techniques that affect the renal parenchyma or vasculature, presumably leading to hypertension.[43]

Because hypertension is closely correlated with PAN and had not previously been reported to occur in ACI/SegHsd rats, we considered the possibility of the role of CPN and hypertension. The salient features of CPN in rats include glomerulosclerosis with severe proteinuria and decreased glomerular filtration rate.[14] Decreased blood volume activates the renin–angiotensin–aldosterone system, the end result being increased reabsorption of sodium with concomitant increased reabsorption of water, thereby elevating blood volume and pressure. However, we did not find a significant association between the presence of CPN and PAN in these rats. Further, the rats in this study were already deceased upon receipt for postmortem evaluation, and blood pressure was not recorded antemortem as part of the original study.

We also considered a possible relationship between PAN, hypertension, and cardiac valvular cartilage formation. One proposed etiology for the formation of cartilage in cardiac valves is related to local mechanical stimulation. In hypertensive animals, increased blood pressure alters blood flow through the vasculature, resulting in turbulence and local mechanical strain on the vessels or valves. Mechanical forces are thought to induce the transformation of cells into cardiac chondrocytes.[24,30] Cartilage formation in the heart has been reported to occur in other mammals, such as sheep with implanted prosthetic valves, dogs with pathologic conditions, and Syrian hamsters, possibly as a mechanism to prevent constriction and improve blood flow in coronary arteries during hibernation.[30] The formation of cardiac cartilage also has been described to occur in humans with conditions such as aortic stenosis and valve replacement. However, we found no significant association between PAN and the incidence of valvular cartilage.

PAN and related conditions, although uncommon in domestic animals, have been noted in laboratory animals and humans (Table 3); an immune-mediated etiology is suspected. The conditions in mice (necrotizing polyarteritis) and dogs (beagle pain

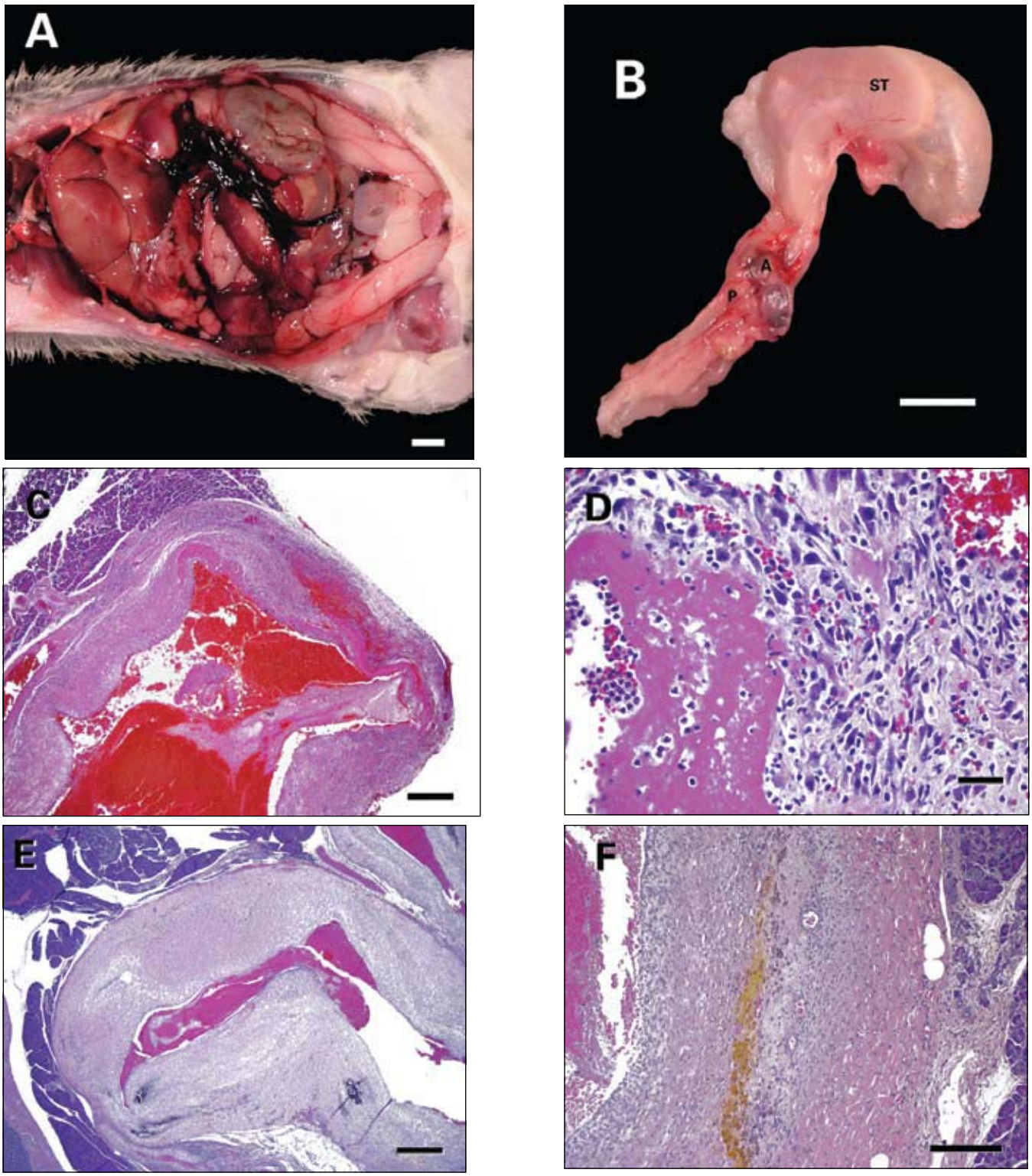


**Figure 2.** Macroscopic and microscopic appearance of grade 3 PAN in the pancreaticoduodenal artery of aged, male ACI/SegHsd rats. (A) Hemoabdomen secondary to severe PAN with vascular rupture is represented by a large hematoma in the left cranial quadrant of the abdomen. Bar, 1 cm. (B) Aneurysmal dilatation (A) of the cranial pancreaticoduodenal artery. ST, stomach; P, pancreas; bar, 1 cm. (C) PAN with subintimal fibrinoid necrosis and mural neutrophilic inflammation and hemorrhage. Hematoxylin and eosin stain; bar, 300 µm. (D) PAN with a fibrin thrombus adhered to the eroded intimal surface and mural infiltrates composed of neutrophils, lymphocytes, plasma cells, and fibroblasts. Hematoxylin and eosin stain; bar = 30 µm. (E) PAN with narrowing of the vascular lumen and mural thickening due to marked intimal hyperplasia. Multiple foci of mineralization (bottom) are present. Hematoxylin and eosin stain; bar, 600 µm. (F) PAN with marked intimal hyperplasia, fibrosis, and aggregates of hemosiderophages. Hematoxylin and eosin stain; bar, 200 µm.

**Table 3**. Summary of PAN and related lesions in selected species

| Species or strain | Disease or condition | Most frequent distribution | Clinical signs | Pathology | Reference(s) |
|---|---|---|---|---|---|
| Mouse (B6C3F1, RF, Hypertensive strains: C57BL, NZB, CPB) | Necrotizing arteritis | Pancreatic, mesenteric, spermatic, middle/inner ear | Generally diagnosed on necropsy, vestibular disease | Inflammation, fibrinoid necrosis, thrombosis, fibrosis, aneurysmal dilatation | 27,34,44 |
| Rat (SHR, SD, ACI/SegHsd) | Polyarteritis nodosa | Mesenteric, pancreatic, testicular | None, acute death with rupture and hemoabdomen | Fibrinoid necrosis, inflammation, fibrosis, thrombosis, dissection, rupture | 7,27,29,39,43 |
| Dog | Beagle pain syndrome, canine juvenile polyarteritis syndrome | Cervical spinal cord mediastinal, heart | Fever, anorexia, hunched stance | Perivascular nodules of inflammation, thrombosis | 17,23,36,38 |
| Nonhuman primate (*Macaca fasicularis*; 2 case reports) | Polyarteritis nodosa | Kidney, small intestine, colon, heart, spleen, mesentery, bladder, pancreas | Lethargy, dehydration, fever, renal failure, anemia | Segmental arteritis, fibrinoid necrosis | 2,28 |
| Human | Polyarteritis nodosa, infantile polyarteritis nodosa, Kawasaki disease | Renal, hepatic, gastrointestinal, heart | Fever, abdominal pain, hypertension, vascular rupture | Necrotizing vasculitis with fibrinoid necrosis, thrombosis | 8,9,22,32,35 |

syndrome) have been described extensively.[36,37] Sporadic cases in nonhuman primates, cats, horses, cattle, sheep, deer, mink, and pigs have been reported.[3,7,15,28]

Necrotizing polyarteritis occurs both as a spontaneous and an experimentally induced disease in mice. Several strains, including B6C3F1, RF, and various hypertensive strains (C57Bl, NZB, and CPB), have a higher occurrence of natural disease than others.[34] In mice, the incidence of disease is higher in males than females and increases with age.[34] The location of lesions in the mouse is similar to that in the rat and includes pancreatic, mesenteric, and spermatic arteries.[34] However, mice also have a high incidence of affected vessels around the middle and inner ears that manifests clinically as a vestibular syndrome (head tilt and circling).[27]

Beagle pain syndrome has been described to occur in colonies of research beagles [1,17,36,38] as well as individual pet dogs. The syndrome presents clinically as intermittent neck pain with fever seen most commonly in young (4 to 9 mo) beagles.[42] The primary vessels affected are arteries in the cervical spinal cord, mediastinum and heart. Lesions in the lung, thymus, stomach, thyroid and adrenal glands, and testes also have been reported.[23] Concurrent amyloidosis has been found in several affected research beagle colonies.[36] The canine juvenile polyarteritis syndrome that primarily affects vessels in the heart is used as a model for Kawaski disease in humans in light of the distribution, age of onset, and histologic features.[11,36]

There are 2 published case reports of PAN in nonhuman primates, both in cynomolgus macaques (*Macaca fasicularis*).[2,28] In both cases, the affected vessels were located in the kidneys, small and large intestines, mesentery, and pancreas, with noted sparing of the pulmonary vessels. Histologically, small- to medium-sized vessels were affected in a segmental fashion in various stages of severity. This distribution of affected vessels and microscopic appearance is similar to the lesions noted in humans.

In humans, PAN occurs most frequently in kidneys, heart, liver, gastrointestinal tract, and testes but can be found in any organ (with the exception of the lungs).[9] PAN is classically a disease of young adults but can occur at any age and appears to affect men more frequently than women. Clinical signs are related to the location of the organs affected but most frequently manifest as peripheral neuropathy and gastrointestinal symptoms. PAN also can present with vague symptoms such as fever, malaise, weight loss, and hypertension. Kawasaki disease is a specific form of PAN that occurs in children, primarily in Japan, and principally involves coronary arteries. The etiology of PAN in humans is thought to be immune-mediated, as in other species, and is categorized as either idiopathic or secondary to a known cause, usually hepatitis B virus. The histopathology of PAN in humans is very similar to that in other species but demonstrates notably less fibrinoid vascular necrosis.[32]

The presentation of PAN as hemoabdomen secondary to arterial rupture is not recognized in animals but is a common sequela in human cases. There are numerous case reports of hemoabdomen in people that have occurred secondary to rupture of vessels affected by PAN, including middle colic, mesenteric, splenic, and hepatic arteries.[8,10,18,19,22,33] More than 50 cases of ruptured renal aneurysms with perirenal hemorrhage have been reported.[35] Other reported locations of vascular rupture in humans with PAN include coronary, aortic, tibial, and cerebral arteries.[16,17,20,40] To our knowledge, this report is the first description of hemoabdomen resulting from ruptured PAN lesions in rats.

Rupture of the pancreaticoduodenal artery and hemoabdomen secondary to PAN was prevalent in this population of aged ACI/SegHsd rats and should be considered as a cause of unexpected death in aging rat studies. The distribution and severity

of PAN lesions reported here is similar to previous findings of PAN lesions in SHR rats. Percentage of fat in the diet did not affect the incidence of PAN or the severity of PAN lesions resulting in vascular rupture. There was also no association between the percentage of dietary fat and the occurrence of CPN or valvular cartilage formation. Blood pressure monitoring in aging rats is recommended to aid in determining whether hypertension is a pre-existing factor, possibly secondary to CPN, leading to PAN or a sequela of PAN.

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