Pancreatic Islet Hyperplasia: A Potential Marker for Anabolic-Androgenic Steroid Use

Jared Weinand, Walter L. Kemp

ABSTRACT

It has been estimated that up to four million Americans have used anabolic-androgenic steroids (AAS) to increase muscle mass – either for improved athletic performance, enhanced personal appearance, or both. While the pathologic effects of supra-physiologic doses of AAS have been well-described for some organ systems, such as the cardiovascular system, the effects on other organ systems are less well-described; for example, there is a dearth of knowledge in the medical literature regarding the effects of recreational use of AAS on the islet cells of the endocrine pancreas. As pancreatic islet hyperplasia has previously been described in the literature in a group of patients receiving long-term AAS treatment for Fanconi anemia, it is reasonable to suggest that the use of AAS by bodybuilders could produce the same (or similar) histologic changes. We present a case that offers support for the association of anabolic-androgenic steroid use and pancreatic islet hyperplasia. *Acad Forensic Pathol. 2018 8(3): 777-785*

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No identifiable personal data were presented in this manuscript

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INFORMATION

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INTRODUCTION

Anabolic-androgenic steroids (AAS), which comprise testosterone and many synthetic chemical derivatives of testosterone, are the most commonly used pharmacologic agents from the larger category of performance-enhancing drugs (PED) (1, 2). While competitive athletics is often associated with the use of AAS, it has been estimated that nearly 80% of contemporary users of AAS are recreational weightlifters (3). The number of individuals using AAS is high. Sagoe et al., based upon their review of the literature, determined that the overall lifetime prevalence rate for the use of AAS by males in North America is 3.0% (4). In the United States, two million individuals are either currently using or have used AAS (5).

While the use of AAS increases skeletal muscle mass by inducing hypertrophy of both type 1 and type 2 skeletal muscle fibers (6), which would represent the most likely reason they are abused by competitive athletes and recreational weightlifters, they also have effects on other organ systems. In the cardiovascular system, AAS cause substantial hypertrophy of human cardiac myocytes, alter lipoprotein metabolic pathways, and directly damage the endothelium. Alteration of the lipoprotein metabolic pathways can cause an increased risk and premature propensity for atherosclerosis, and damage to the endothelium can lead to tissue ischemia (1). While the pathologic effects of AAS usage on the cardiovascular system have historically received the most attention in the literature (1, 3, 7), other organ systems can be affected. Anabolic-androgenic steroid use causes decreased glucose tolerance, which indicates the potential for the pancreas to be affected; however, Lusetti et al. reviewed the autopsies for six individuals who used AAS and examined the brain, heart, liver, lungs, and kidneys and Frati et al. reviewed 19 fatal cases associated with AAS from the medical literature, but neither study indicated any findings related to pathologic changes in the pancreas (1, 7).

The endocrine function of the pancreas is derived from five different cell types: α, β, δ, ε, and PP cells, which produce glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide respectively, all of which are located in histologically-distinct groupings classically termed islets of Langerhans (8). Under certain situations, a reactive hyperplasia of the pancreatic islets can occur. One source of a reactive islet hyperplasia is AAS used to treat Fanconi anemia (9). Islet hyperplasia can be identified via histologic examination of the pancreas. In the literature, the standard pancreatic islet diameter has been described as around 150 μm, with islets measuring >250 μm in diameter generally considered to be hyperplastic (8, 10).

This paper presents the death of a known professional bodybuilder with pancreatic islet hyperplasia identified upon histologic examination of the pancreas. Based upon information available in the medical literature (i.e., how common AAS usage is and the associated of AAS use and pancreatic islet hyperplasia), the most likely source of the pancreatic islet hyperplasia in this case was the use of AAS. Further exploration of this potential association in a larger case series would be prudent, as islet hyperplasia could provide a more reliable and specific histologic marker of AAS use than would cardiac hypertrophy or the other described cardiac effects.

CASE REPORT

A male in his 30s with recent legal trouble and potential pending job loss purposefully stepped in front of a train and received multiple blunt force injuries of the head and trunk. The manner of death was certified as suicide.

At autopsy, the decedent was a well-nourished and muscular male (**Image 1**). His blunt force injuries included a basilar skull fracture (**Image 2**) and a gaping 23 cm laceration of the left side of the back with underlying rib fractures (**Image 3**), together resulting in partial avulsion of this portion of the body. Routine microscopic examination of the pancreas revealed hyperplastic islets. Also, on gross and microscopic examination, moderate to focally severe coronary artery atherosclerosis (resulting in an estimated 65-75% stenosis of the lumen of the vessel) was found. The coronary artery atherosclerosis was predominantly

intimal fibrosis with minimal underlying atheromatous material (i.e., little intracellular and extracellular lipid in the plaque). Femoral blood and vitreous fluid both tested positive for ethanol (0.231 g/dL and 0.238 g/dL, respectively); the volatile screen and drug screen were otherwise negative. Directed testing for AAS was not performed.

To confirm the pancreatic islet hyperplasia, microscopic images comprising 12 representative pancreatic islets were obtained with an Olympus BX53 microscope, an Olympus DP27 camera, and the program, Olympus cellSens Standard 1.13. Each microscopic image contained one or more islets. The images were subsequently analyzed with ImageJ to determine the maximum diameter, in micrometers, of each islet (11).

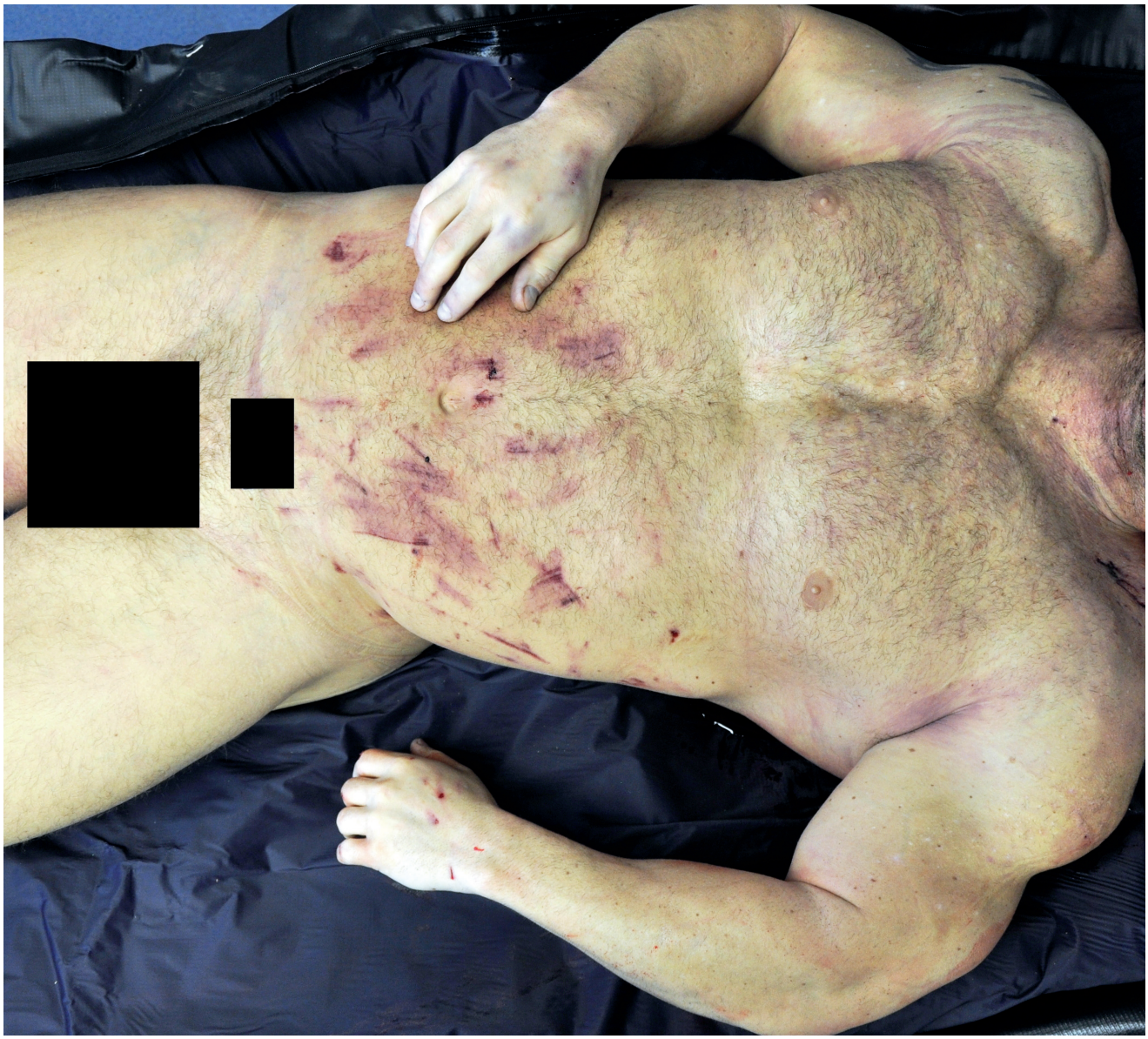

Image 1: The decedent, a well-developed muscular male, who was a professional bodybuilder.

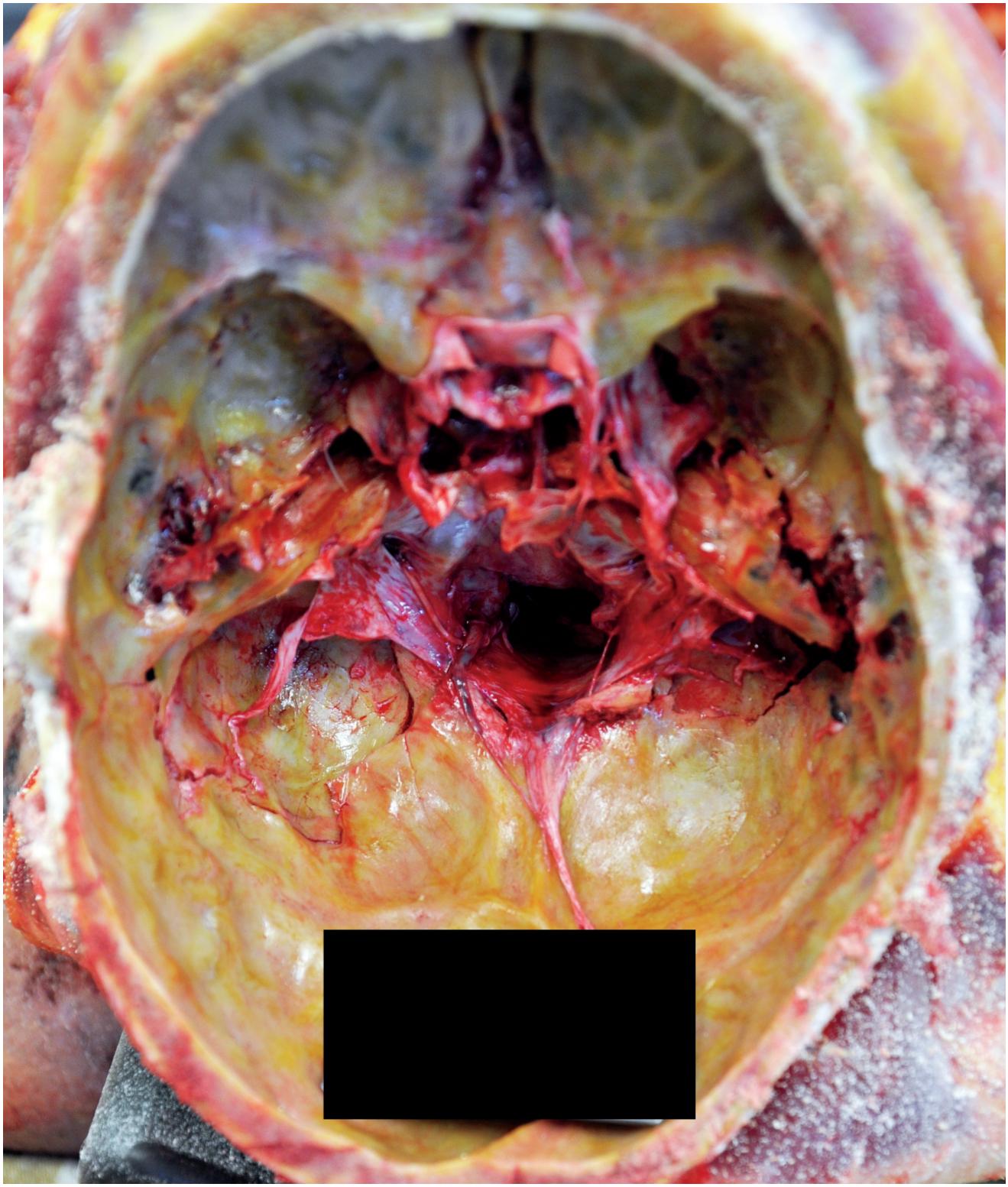

Image 2: Basilar skull fracture.

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The Olympus cellSens standard 1.13 program stamps each image with a standard measurement device that was used for calibration of ImageJ to obtain the required islet diameters. The range of diameters for the pancreatic islets examined was 252 to 910 μm, with a mean of 556.75 μm and a median of 490.5 μm (**Images 4 and 5**). Even given that an islet diameter of >250 μm is considered hyperplastic and each islet measured had a diameter greater than this mark, a Wilcoxon signed rank test was performed to test the hypothesis that the true mean of the islet diameters in the case presented was not equal to 250 μm. The Wilcoxon signed rank test indicated a *p*-value of 0.0004883, further supporting that the islets in the autopsy case presented were definitely hyperplastic. All calculations and statistical analyses were performed using R (12).

DISCUSSION

Novak et al. described pancreatic islet cell hypertrophy and hyperplasia at autopsy in a group of patients with Fanconi anemia who were being treated with AAS (9). Each of the patients had been on AAS therapy for at least 42 months prior to death. The authors observed that the hyperplasia and hypertrophy of the islets was similar to the findings in infants of diabetic mothers (IDM). In IDM, glucose transfer from mother to fetus leads to fetal hyperglycemia, which induces pancreatic islet hypertrophy and β-cell hyperplasia (13). This histologic finding prompted Novak et al. to hypothesize that the islet cell hyperplasia and hypertrophy may be secondary to glucose intolerance, which is a pharmacologic effect of androgen therapy

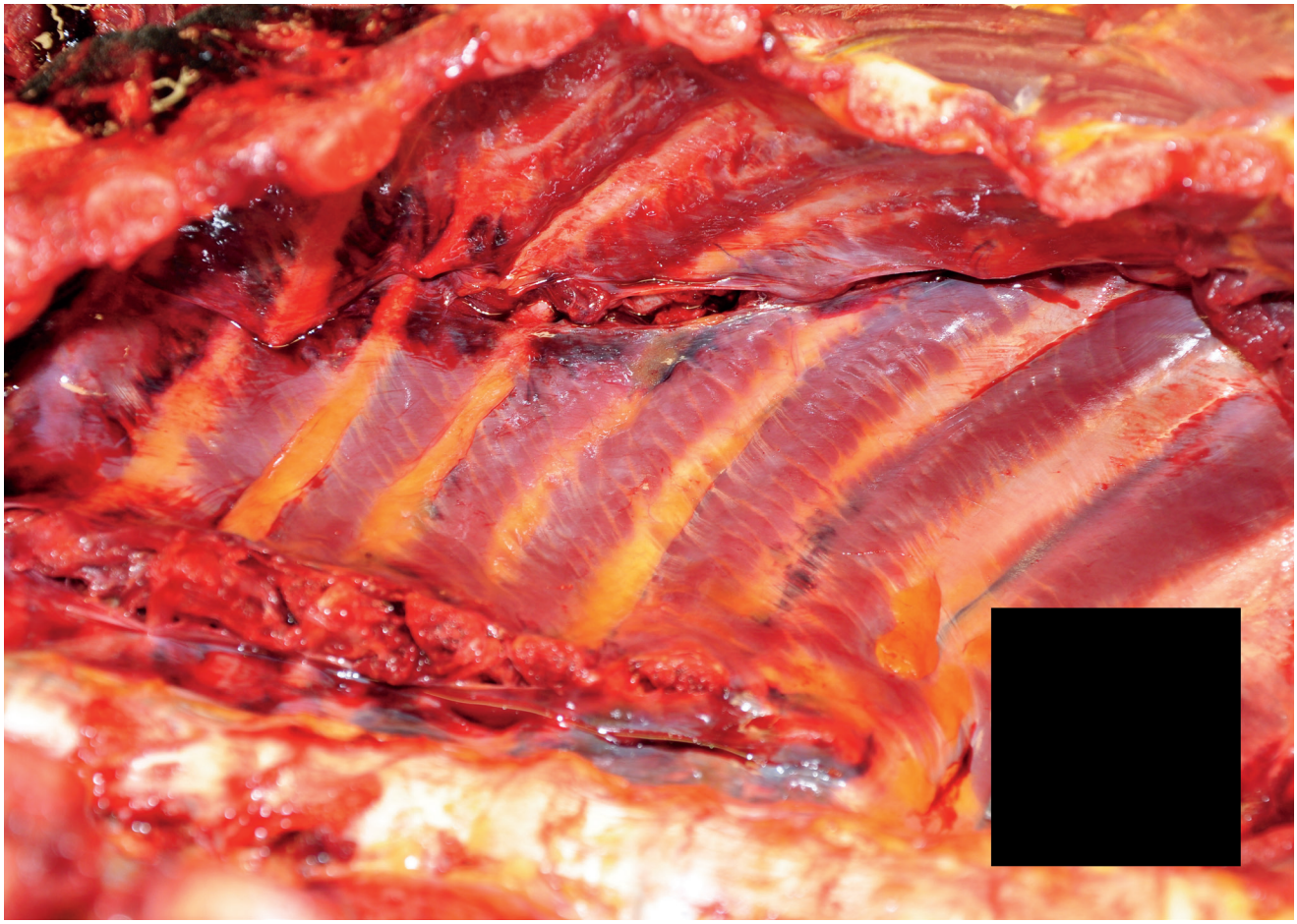

Image 3: Multiple rib fractures.

(7, 9). While hyperglycemia in IDM can induce pancreatic islet hyperplasia, diabetes mellitus in an adult patient most likely does not. While some authors indicate that individuals with insulin resistance or type 2 diabetes can develop pancreatic islet hyperplasia (8), controlled studies have identified that patients with type 2 diabetes mellitus have a decrease in the volume density of β cells, with some studies showing an increase in the volume density of α cells and others showing no statistically significant increase (14). In general, in type 1 diabetes mellitus there is essentially always a reduced number of β cells and in type 2 diabetes mellitus, while the changes are less uniform, there is sometimes a reduced number of β cells, islet fibrosis, and amyloidosis (15). While diabetes mellitus is not clearly a cause of pancreatic islet hyperplasia, other causes of reactive islet hyperplasia include obesity, genetic factors (e.g., GLUT4 deletion, FGF21 deficiency), lipodystrophy, glucocorticoid excess, or use of atypical anti-psychotic medications (e.g., clozapine, olanzapine, risperidone) (16). Chronic laxative abuse has also been associated with pancreatic islet hyperplasia (17).

Additional features of the presented case that are relevant to the topic of the use of AAS are the alcohol consumption, the manner of death, and the coronary artery atherosclerosis. First, AAS usage has been as-

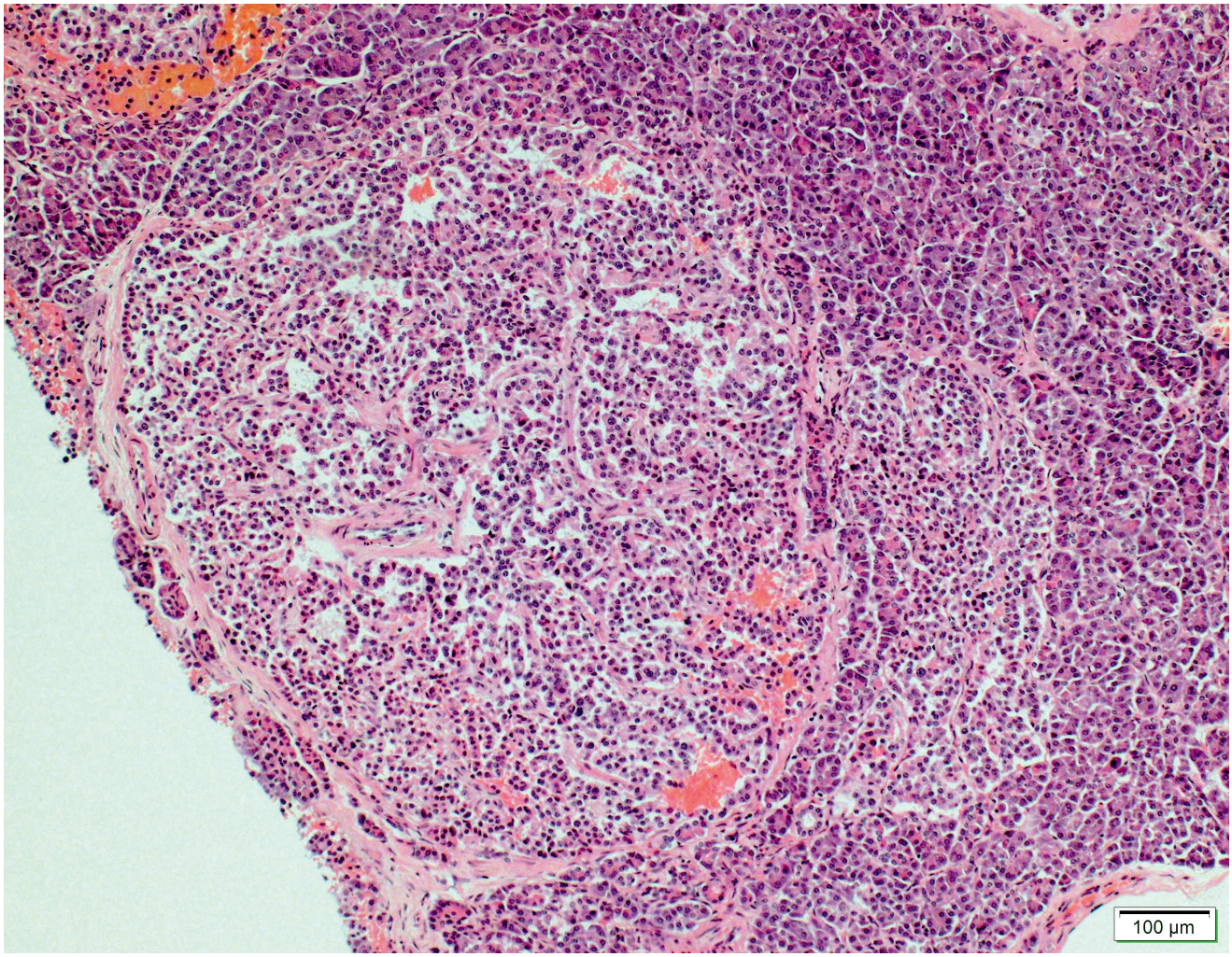

Image 4: Representative pancreatic islets from the decedent (H&E, x100).

sociated with alcohol consumption in both animal and human models, with a proposed mechanism of steroid-induced alterations in the opioid reward system of the brain that causes an increased response to alcohol (2). Anabolic-androgenic steroid usage may also disrupt the balance of the dopaminergic system of the nucleus accumbens, a known contributor to the reward system of the brain. This disruption could promote the rewarding effects of alcohol, leading to additional increases in alcohol consumption (2). Second, psychiatric alterations have been found to have an association with AAS usage. These include hypomanic to manic symptoms, such as reckless behavior, aggressiveness, and hyperactivity. Conversely, withdrawal at the end of a so-called "cycle" of AAS usage has shown psychiatric findings of depressed mood, loss of interest in usual activities, and occasional suicidal ideation. This disinhibition has been hypothesized to be related to AAS-induced alterations in the dopaminergic system of the brain, similar to the effects of alcohol (2). The disequilibrium at the neurotransmitter level is not unlike the effects of typical euphoria-inducing drugs of abuse, though AAS do not cause immediate releases of large amounts of dopamine and, therefore, do not often cause a "high" (18). Both the hypomanic/manic symptoms and the depressed/disinhibited symptoms seen with AAS usage and withdrawal could be pertinent to the case being discussed, as the manner of

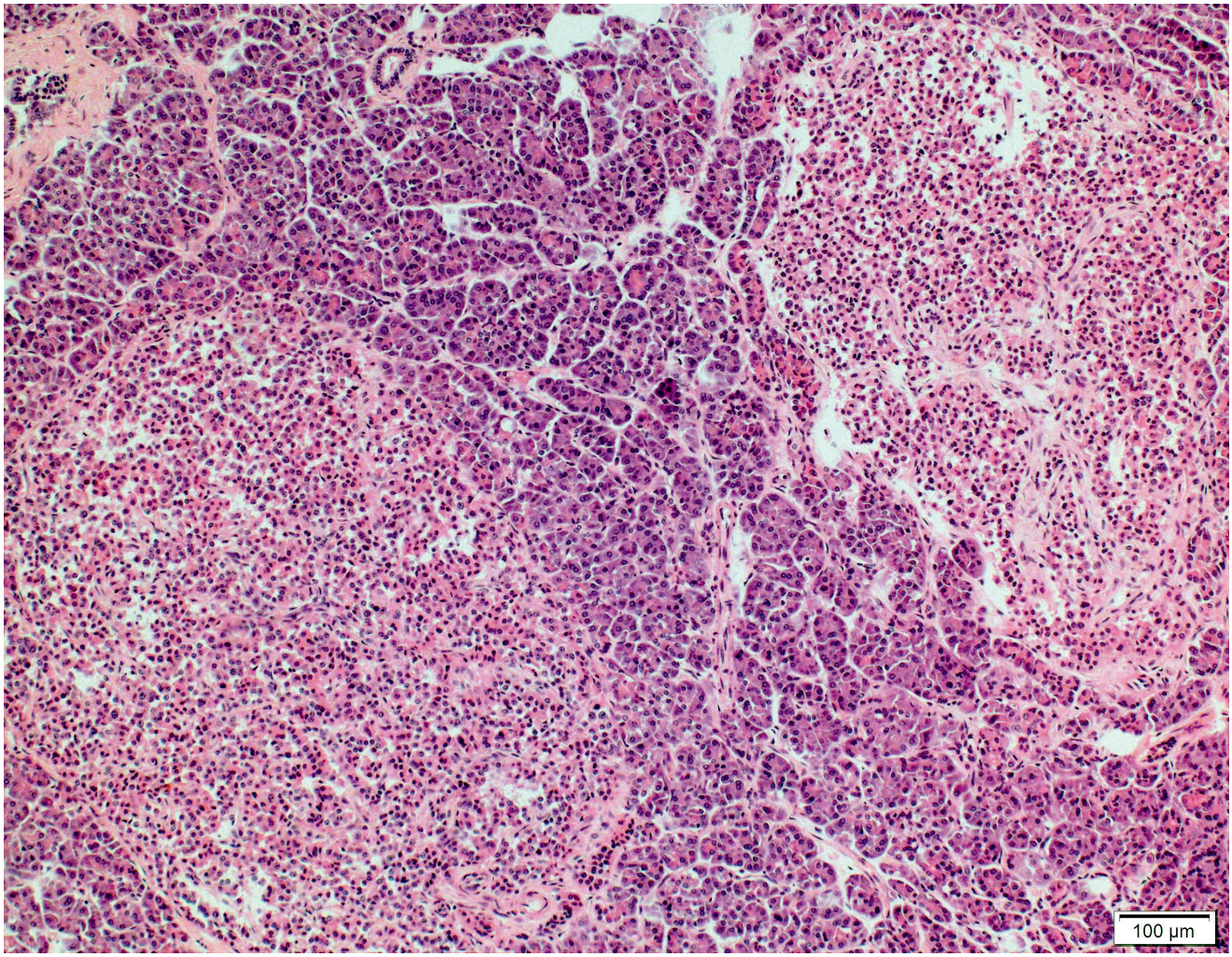

Image 5: Representative pancreatic islets from the decedent (H&E, x100).

death was suicide. Users of AAS have a higher rate of intentional death (defined as suicide or homicide) than users of heroin and/or methamphetamine. This finding that AAS users die significantly more often due to suicide or homicide than users of other drugs suggests a high risk of violent or depressive symptoms among AAS users, even when compared to other drug users (19). Third, the finding of a significantly stenotic site of coronary artery atherosclerosis in an otherwise young healthy male is consistent with the fact that use of AAS can alter lipoprotein pathways and lead to premature atherosclerosis.

While the individual presented in this case was a known bodybuilder with islet hyperplasia discovered incidentally at autopsy, and while islet hyperplasia is a reported side effect of the use of anabolic-androgenic steroids in a therapeutic environment (9), it is not known whether this individual was, in fact, using anabolic-androgenic steroids. Toxicologic confirmation of the presence of AAS would not necessarily assist in the determination of whether or not AAS caused the change in the pancreas. Given that islet hyperplasia is not an acute change, with Novak indicating in their sample that all patients had used AAS for 42 months, toxicology testing at the time of autopsy, if negative for AAS, would not refute AAS as a cause of the change in the pancreas (9). Another consideration in interpreting the microscopic findings in the pancreas is the possible use by this individual of additional anabolic, performance-enhancing, or analgesic drugs such as opioids, insulin, clenbuterol, or human growth hormone, which are commonly found in conjunction with AAS usage (2). The potential effects of these drugs, or others, on the endocrine pancreas should be considered as their possible involvement in this case is unknown and polypharmacy has been suggested to be common amongst AAS users (20); however, a review of the literature does not indicate that opioids, clenbuterol, or human growth hormone are associated with islet hyperplasia, and since patients with type 2 diabetes mellitus have pancreatic atrophy, that the use of insulin would cause significant pancreatic hyperplasia is not certain.

CONCLUSION

In conclusion, even with the above caveats, given that of the performance enhancing drugs, testosterone, and other AAS are most commonly used and that the use of AAS has been associated with islet hyperplasia and hypertrophy in a case series, the most likely cause of the islet hyperplasia in this autopsied case is AAS. Further exploration of this association in a larger case series would be prudent, as islet hyperplasia could provide a more reliable and specific histologic marker of AAS use than would cardiac hypertrophy or the other described cardiac effects of AAS.

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