Diabetes Mellitus

Samantha Wahlers & John Walsh MD*

Background

Diabetes mellitus (DM) encompasses metabolic diseases, type 1 and type 2, that have an underlying chronic hyperglycemia. In type 1 DM, the body's immune system destroys β pancreatic islet cells, which produce insulin. This autoimmune response results in an absolute insulin deficiency and presents in childhood. For a more in depth discussion on Type 1 diabetes see this article. In type 2 DM, the β pancreatic islet cells are dysfunctional leading to impaired insulin secretion. This insulin deficiency is often due to obesity and sedentary habits (for more information see this article). As it pertains to autopsy, diabetes mellitus has become a major cause of death worldwide as well as a contributing factor to death, as associated with other conditions. Diabetic ketoacidosis is the most common cause of death in children and adolescents with type 1 diabetes. In Type 2 diabetes, DKA remains the most common cause of death, but among cases called DKA, Hyperosmolar Hyperglycemia Syndrome (HHS) may be underreported or inaccurately reported. The mortality rate of DKA is estimate at about 1%, while the mortality rate of HHS is estimated as high as 20%.

Other etiologies of diabetes mellitus include

- Maturity Onset Diabetes of the Young (MODY) is caused by a genetic defect that leaves β cells dysfunctional
- Gestational diabetes
- Glucocorticoid-induced diabetes
- Pancreatic pathologies
    - Cystic fibrosis
    - Pancreatitis
- Cushing disease

Diabetes affects multiple organ systems throughout the body. Below is a quick reference table of the major organ systems affected by DM

Organ	Pathophysiology
Eyes	Diabetes can cause several eye problems, the most significant being diabetic retinopathy, which results from damage to the blood vessels in the retina. This can lead to vision impairment and blindness. Other complications include diabetic macular edema, cataracts, and glaucoma.

Cardiovascular system	Diabetes significantly increases the risk of cardiovascular diseases, including coronary artery disease, heart attacks, and heart failure. The combination of high blood glucose levels, hypertension, and dyslipidemia in diabetic patients accelerates the process of atherosclerosis, leading to narrowed and hardened arteries.
Liver	Diabetes increases the risk of non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis. Insulin resistance plays a significant role in the accumulation of fat in liver cells.
Pancreas	Chronic hyperglycemia can lead to β-cell dysfunction and apoptosis, reducing insulin production and worsening hyperglycemia. This creates a vicious cycle that exacerbates diabetes and its complications.
Kidneys	Diabetic nephropathy is a major complication, characterized by progressive kidney damage leading to chronic kidney disease and potentially end-stage renal disease (ESRD).
Nerves	Diabetic neuropathy affects peripheral nerves, leading to symptoms such as pain, tingling, and numbness, particularly in the extremities. Autonomic neuropathy can affect the cardiovascular, gastrointestinal, and genitourinary systems, leading to various functional impairments.
Skin	Uncontrolled diabetes can lead to various skin conditions, including bacterial and fungal infections, diabetic dermopathy, and necrobiosis lipoidica diabeticorum. Poor wound healing is also a common issue, often leading to chronic ulcers and infections.

Advanced glycation end products (AGEs) are the underlying pathophysiology to most of these complications. The excess glucose in the blood covalently binds to plasma

proteins, thereby altering the protein's ability to function in receptor signaling pathways and enzymatic activities. In the setting of arteries, AGEs induce oxidative stress, thereby contributing to atherosclerosis.

Quick Tips at Time of Autopsy

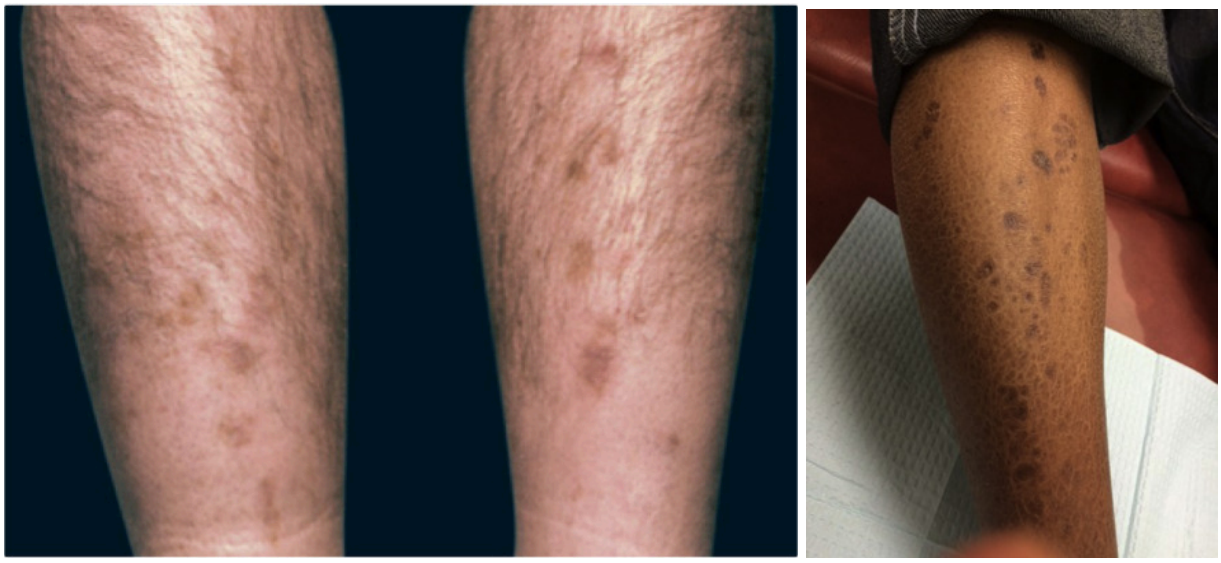
Clinical History

- Should there be any concern for diabetes (DM) as the underlying cause of death, testing of vitreous fluid should be considered. While this ancillary test is discussed below, it is important to explore the possibility of a DM-related death prior to entering the autopsy suite, upon review of the patient's history, so that the appropriate plan is in place to obtain vitreous or other diagnostic tissues
    - Death, as a 1st presentation of diabetes, should be considered particularly in the extremes of age in the correct clinical circumstances such as: medical history of "seizure," "convulsions," "coma," or altered mental status, weight loss, unquenchable thirst, "smelled funny" all should prompt consideration of diabetes in the differential and subsequent appropriate exam (including possible vitreous studies).
- Laboratory Diagnostic Criteria for DM
    - Hemoglobin A1c (HbA1c) ≥ 6.5%
    - Fasting plasma glucose ≥ 126 mg/dL
    - 2-hour plasma glucose ≥ 200 mg/dL during oral glucose tolerance test (OGTT)
    - Patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose ≥ 200 mg/dL
    - In absence of clear hyperglycemia, diagnosis requires 2 abnormal test results from same sample or 2 separate test samples
- Kidney function testing using urine analysis to look for microalbuminuria and ketonuria
- Blood work to detect antiglutamic acid decarboxylase antibodies
    - For type 1 DM
- Antemortem physical exam findings for complications including
    - Diabetic retinopathy
    - Diabetic nephropathy
    - Diabetic neuropathy
    - Necrobiosis lipoidica

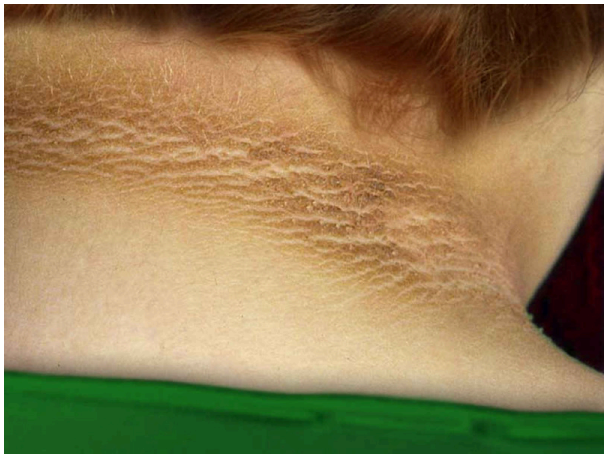
External Exam

- Body Habitus: obesity or marked weight loss could be indicators of Type 2 and Type 1 Diabetes, respectively.
- Infections: increased susceptibility to bacterial and fungal skin infections.
- Signs of Poor Circulation: peripheral edema, particularly in the legs and feet, with or without stasis dermatitis.
- Dermatopathic evidence of Peripheral Vascular Disease
    - Skin tags: associated with insulin resistance and may be seen in pre-diabetics as well

    - Diabetic Dermopathy: brownish patches on the skin, usually on the shins
    - Acanthosis Nigricans: dark, velvety patches, often found in body folds and creases
    - Necrobiosis Lipoidica: yellow, waxy areas on the skin, often on the lower legs
    - Diabetic Foot Ulcers: open sores on the feet due to poor circulation and neuropathy.
        - Poor wound healing: presence of chronic, non-healing wounds or scars indicating slow healing processes.
        - Amputations: missing toes, feet, or lower limbs due to severe infections or gangrene secondary to diabetic complications.
- Neuropathy: deformities such as Charcot foot (joint dislocation and fractures in the foot) might be visible externally.



Images: (Left) Pigmented pretibial patches in a patient with diabetes known as diabetic dermopathy. (Right) Diabetic dermopathy on a darker skin complexion. (Image credits: (Left) Angelina Labib from Skin Manifestations of Diabetes Mellitus. (Right) Sam Gorelik from Science Direct).




Images: (Left) Poorly demarcated hyperpigmented patches called acanthosis nigricans pictured on a lighter skin complexion. (Right) Acanthosis nigricans on a darker skin complexion. (Image credits: (Left) Scott Dulebohn from StatPearls. (Right) Shyam Verma from StatPearls).

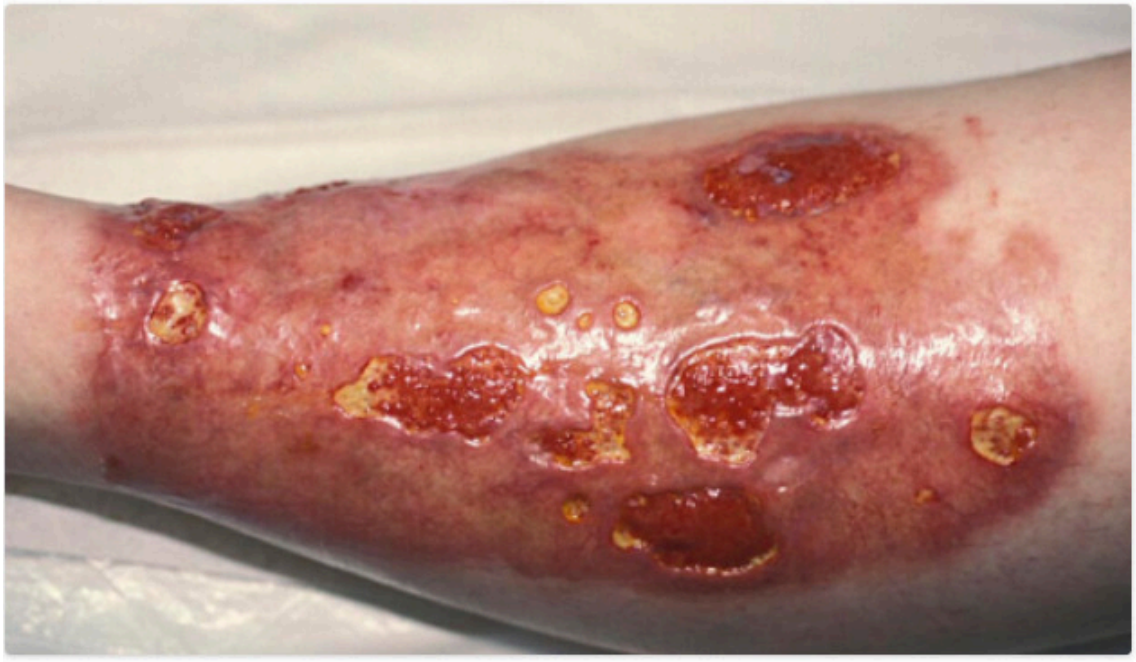


Image: Demarcated erythematous papules and plaques called necrobiosis lipoidica (Image credit: Angelina Labib from "Skin Manifestations of Diabetes Mellitus").

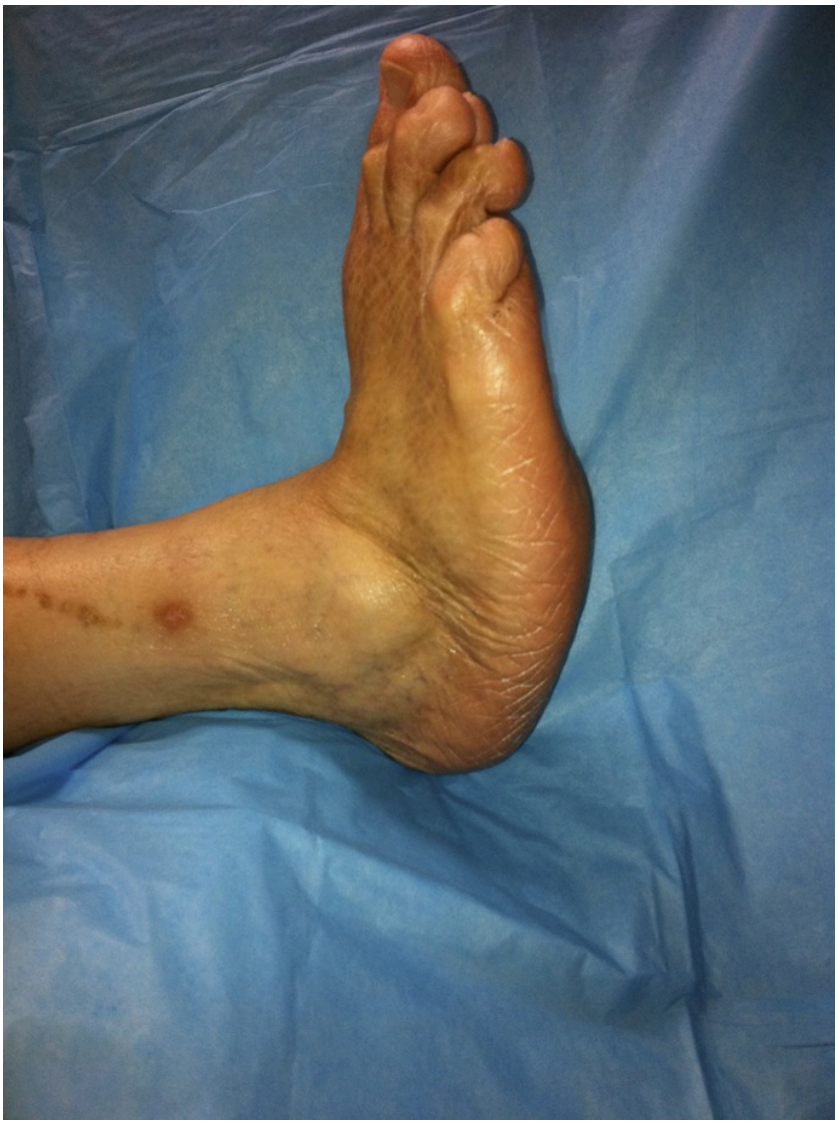


Image: Rocker bottom deformity called charcot foot in a patient with diabetes mellitus (Image Credit: Lee Rogers from "The Charcot Foot in Diabetes")

Ancillary Testing

- Testing of vitreous electrolytes should be considered in deaths without immediately evident cause of death [found down, or found dead in bed], or where a traumatic cause of death may have been predisposed by a natural event [motor vehicle collision]. While many of these scenarios will be forensic cases, they can present in hospital cases as well.
- Collecting vitreous
    - This can be done even when decomposition is present.
    - Collection goals: minimum of 1mL of clear translucent vitreous fluid.
        - Fluid can be aggregated into **1 Red top tube** (R & L eye together) or, if sufficient fluid or if fluid from 1 eye is cloudy, collected R eye / L left eye.

        - **If gray top tubes are used, the quantitative results for sodium and/or potassium will be affected.**
    - Storage: short term storage in a refrigerator is sufficient, but long term storage requires freezing at -70^{0}F
- Multiple serum markers may also be useful
    - Glycated hemoglobin (use a lavender top tube)
    - Serum beta-hydroxybutyrate (use a red or gold top tube)
    - Serum isopropyl alcohol (use a gray top tube)
    - Serum C reactive protein (use a red or gold top tube)
- Urine glucose
- CBC: may indicate stress reaction and / or evidence of infection. Recent infection has been identified as a predisposing risk factor for HHS.
- While not done routinely in autopsy, it is possible to undertake advanced testing if indicated
    - Immunofluorescence demonstrates linear IgG & albumin on glomerular basement membrane in the kidney.
    - Electron Microscopy demonstrates thickening of glomerular basement membrane (> 600 nm thick) and/or lucent foci on the periphery of mesangial sclerosis.
- Immunohistochemistry
    - WT-1 stain for podocytopenia
    - Decreased amount of Beta and Alpha cells in the pancreas

Internal Examination

- **Arteries:** the vascular consequences of diabetes are generally grouped into microvascular and macrovascular. Microvascular disease results in pathologies such as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy - detailed individually by organ system below. Macrovascular complications of diabetes include **atherosclerosis** which can result in complications such as stroke, myocardial infarction, and peripheral artery/vascular disease.
- **Pancreas**: progressive changes in DM1 and DM2 lead to a small pancreas (*DM1 > DM2*). Atrophy of the pancreatic tissue is more associated with DM1 due to autoimmune destruction of β-cells. In contrast, loss of mass is associated with *fibrosis and lipomatosis* in DM2 as a result of chronic hyperglycemia and associated metabolic stresses. In DM2 this can give the contour of the pancreas a serrated appearance.
- **Kidneys**: in the early stages of diabetes, kidneys may be enlarged due to hyperfiltration and hypertrophy of the nephrons as they try to compensate for increased glucose load. This is often more pronounced in the early stages of DM1. Over time, as diabetic nephropathy progresses, kidneys can become smaller due to the loss of functional renal tissue and the development of fibrosis. The surface of the kidneys may appear granular or nodular in advanced stages due to the presence of glomerulosclerosis and interstitial fibrosis. This granular appearance is not specific and can also be seen with hypertension and other causes of nephrosclerosis. Of note, DM lesions are not uniform between individuals or even within the same individual.

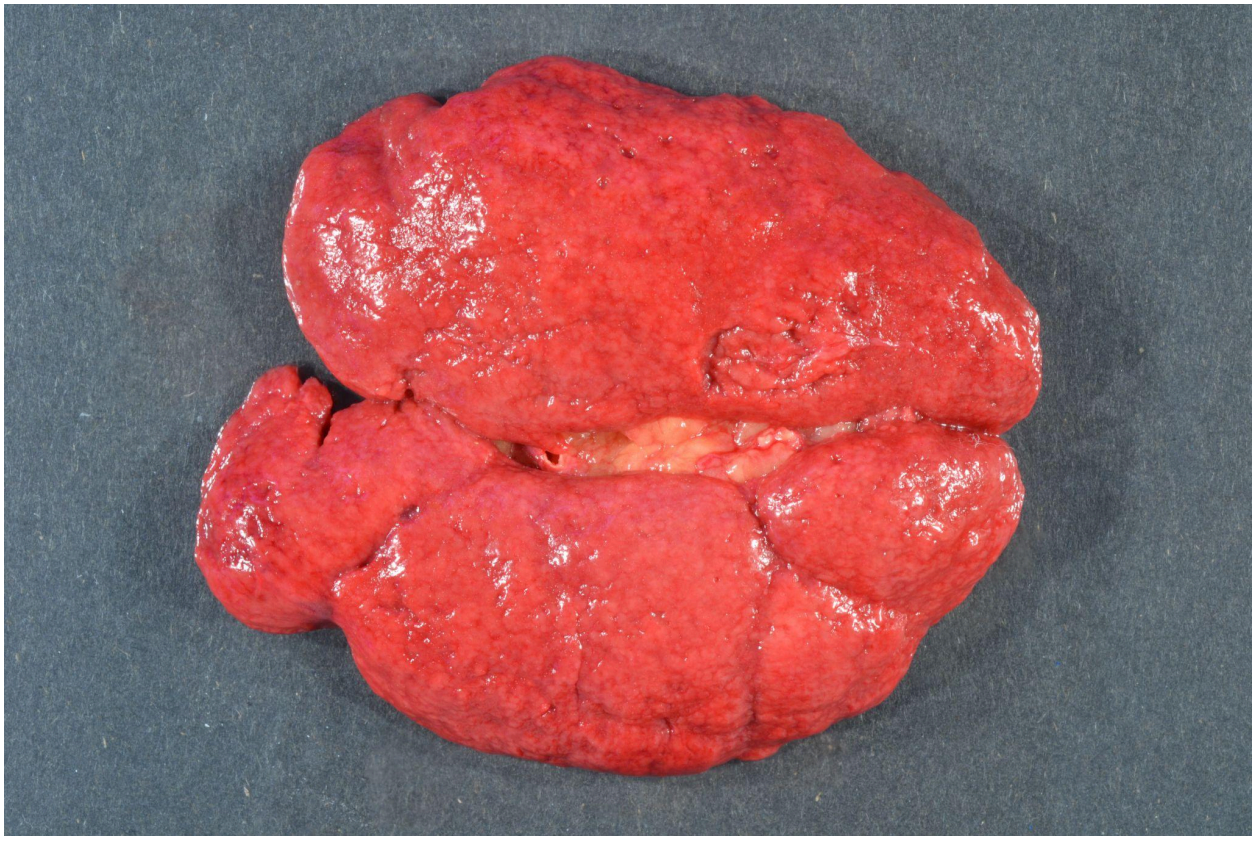


Image: A bisected kidney with cortical granularity and pitting suggestive of underlying glomerulosclerosis. (Image credit: Meagan Chambers/University of Washington).

- **Liver:** changes in the liver happen as a consequence of both direct effects from diabetes as well as secondarily from associated hyperlipidemia, these include hepatomegaly, hepatosteatosis, and, in advanced cases, fibrosis and cirrhosis.

Quick Tips at Time of Histology Evaluation

Pancreas

- Type I DM: early disease is marked by irregularly shaped islet cells and lymphocyte infiltration. Later disease is marked by interlobular and interacinar fibrosis and exocrine atrophy.
- Type II DM: perilobular and intraacinar fibrosis, a reduced number of regularly shaped islets, and amyloidosis (evaluate with a congo red stain).

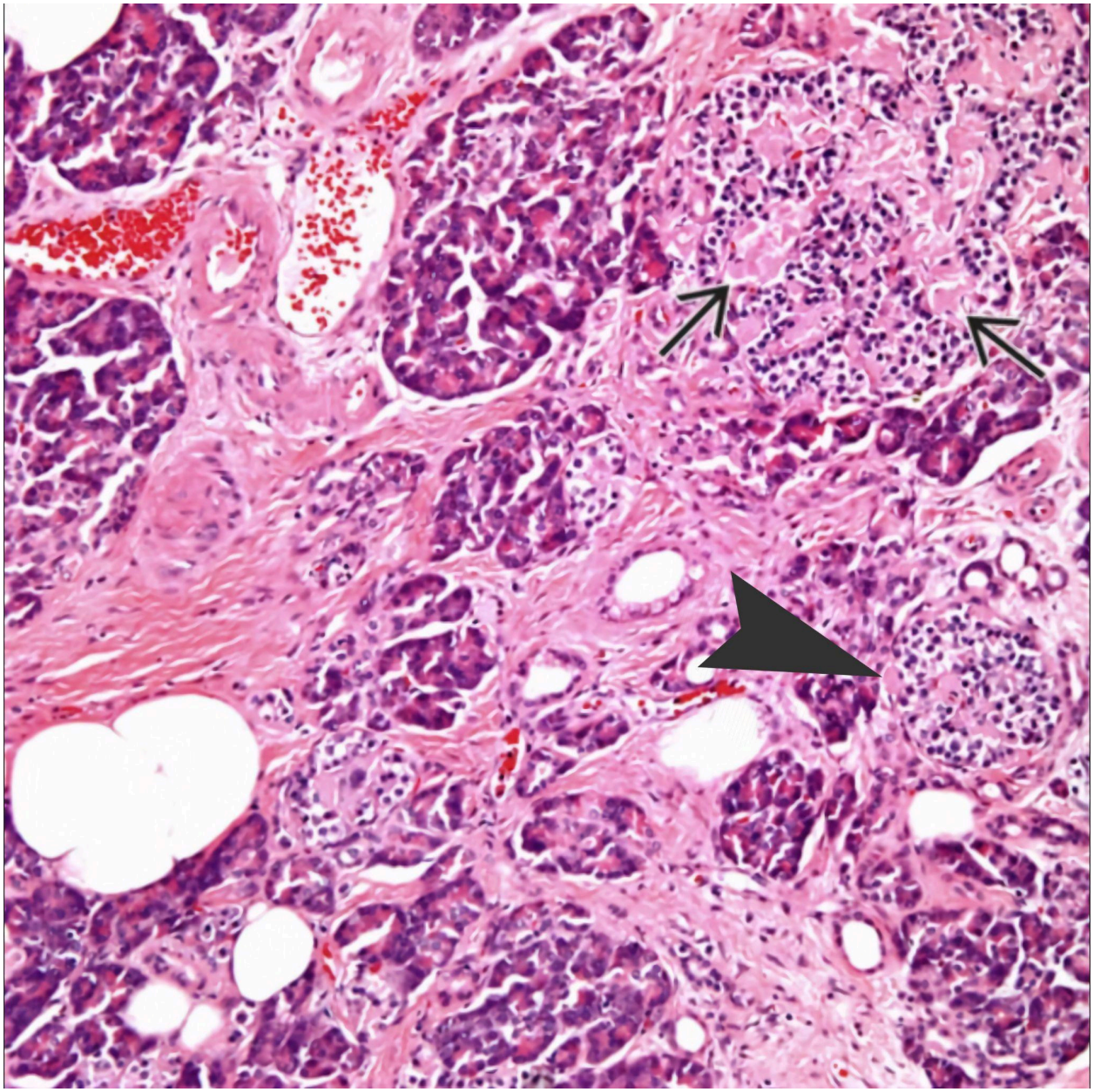


Image: This section from the pancreas of a patient with diabetes shows variably sized islets (thin arrow and thick arrowhead) with focal amyloid deposition (thin arrow), focal fat, and increased interacinar fibrosis. (Image credit: Laura Lamps, ExpertPath).

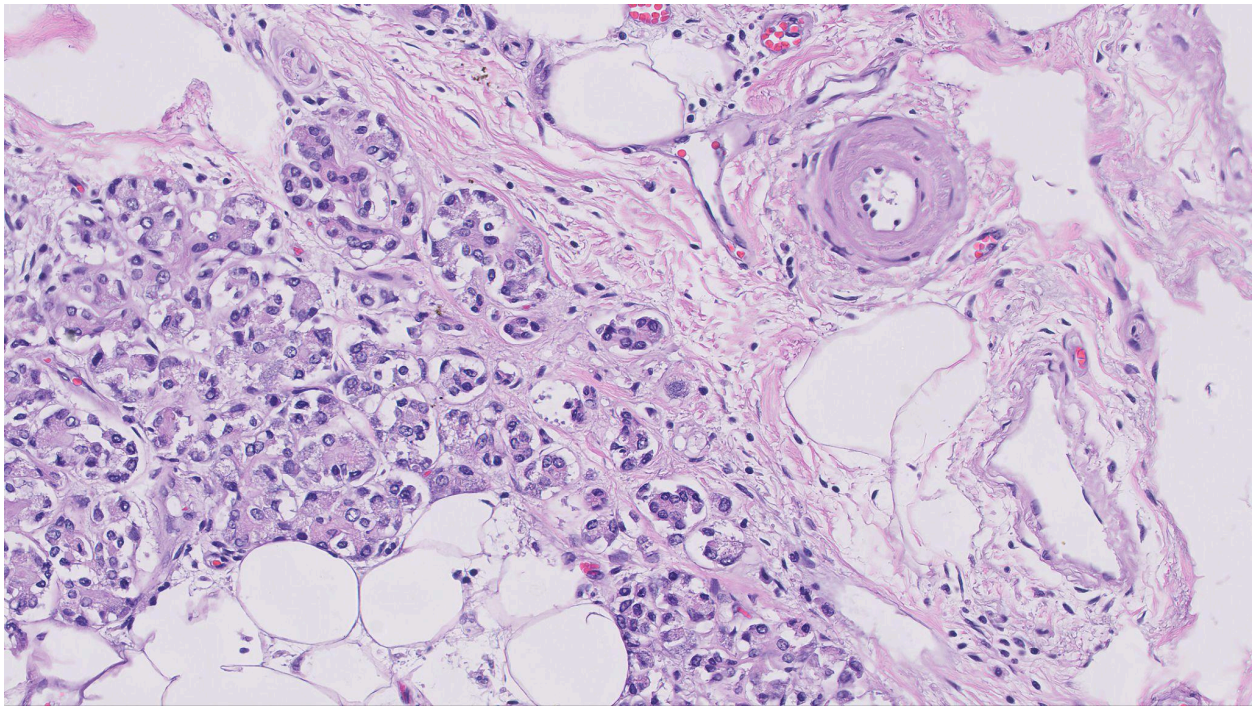


Image: Hyaline arteriolosclerosis can be seen in many organs including spleen (shown here), but also eyes, kidney, etc. (Image credit: Meagan Chambers/Stanford University).

Kidney

- The key histologic finding in diabetic nephropathy will be prominent arterial hyalinosis (note, in DM this will be present in the afferent and efferent arterioles, unlike in hypertension which is only see in the afferent arteriole)

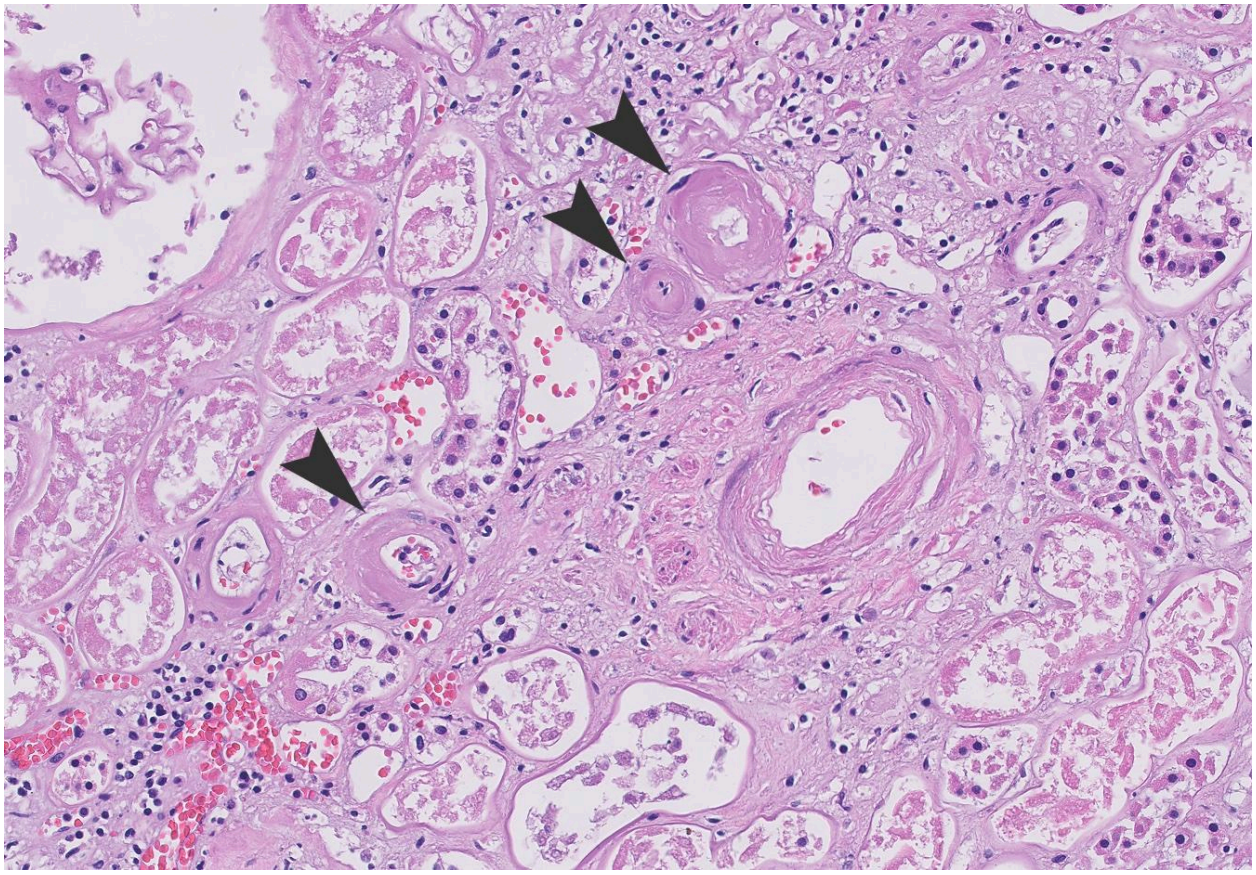


Image: Hyaline arteriolosclerosis can be seen in many organs and is classically identified in the kidney. (Image credit: Meagan Chambers/Stanford University).

- Kimmelstiel-Wilson nodules and mesangial sclerosis (supported by PAS and/or Jones methenamine silver stains); acellular lesions with a hyaline like core, which may indicate long-standing diabetes. Hypercellular mesangial proliferation may also be seen.

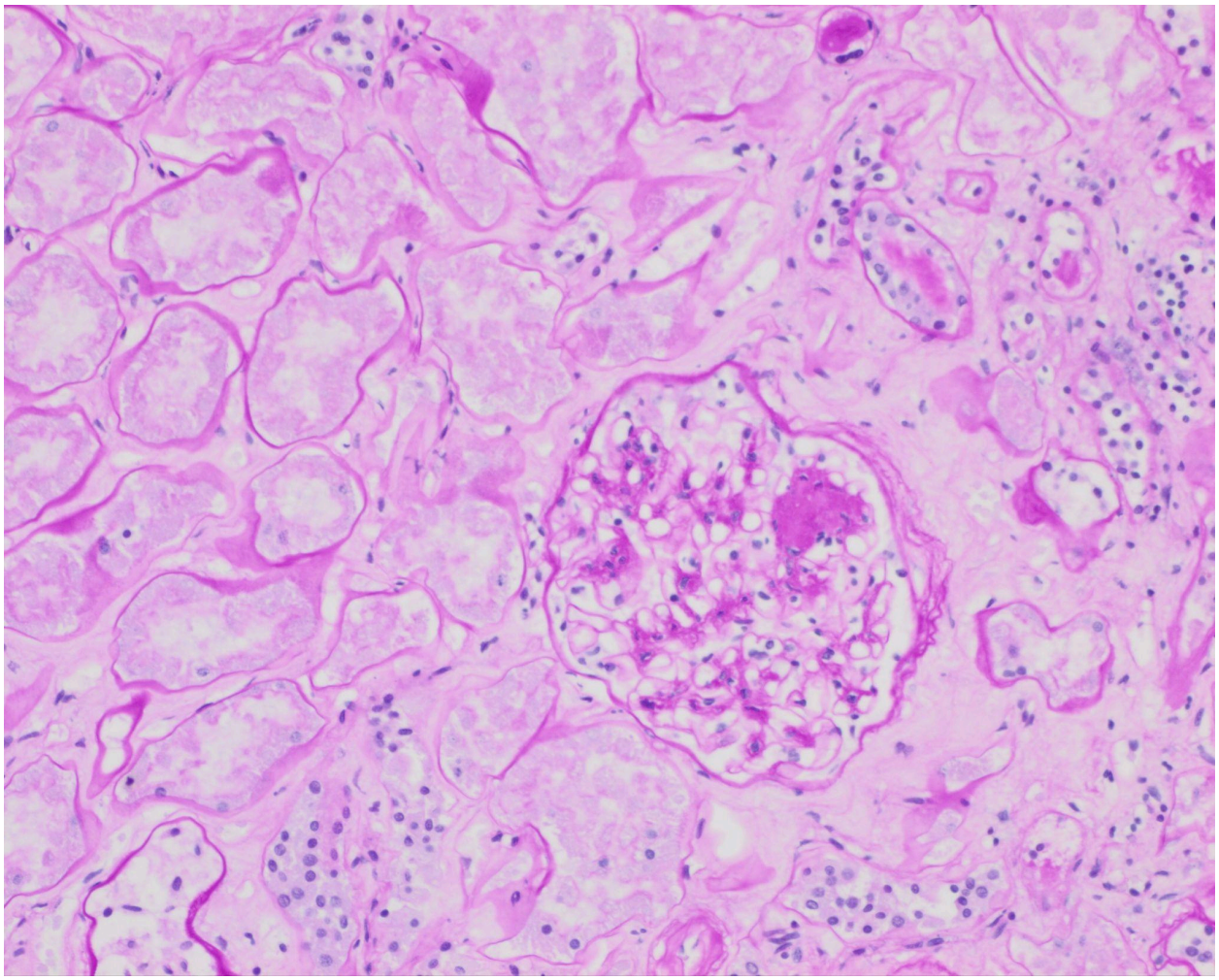


Image: Kimmelstein-Wilson nodule in a glomerulus, PAS staining. (Image credit: Meagan Chambers/University of Washington).

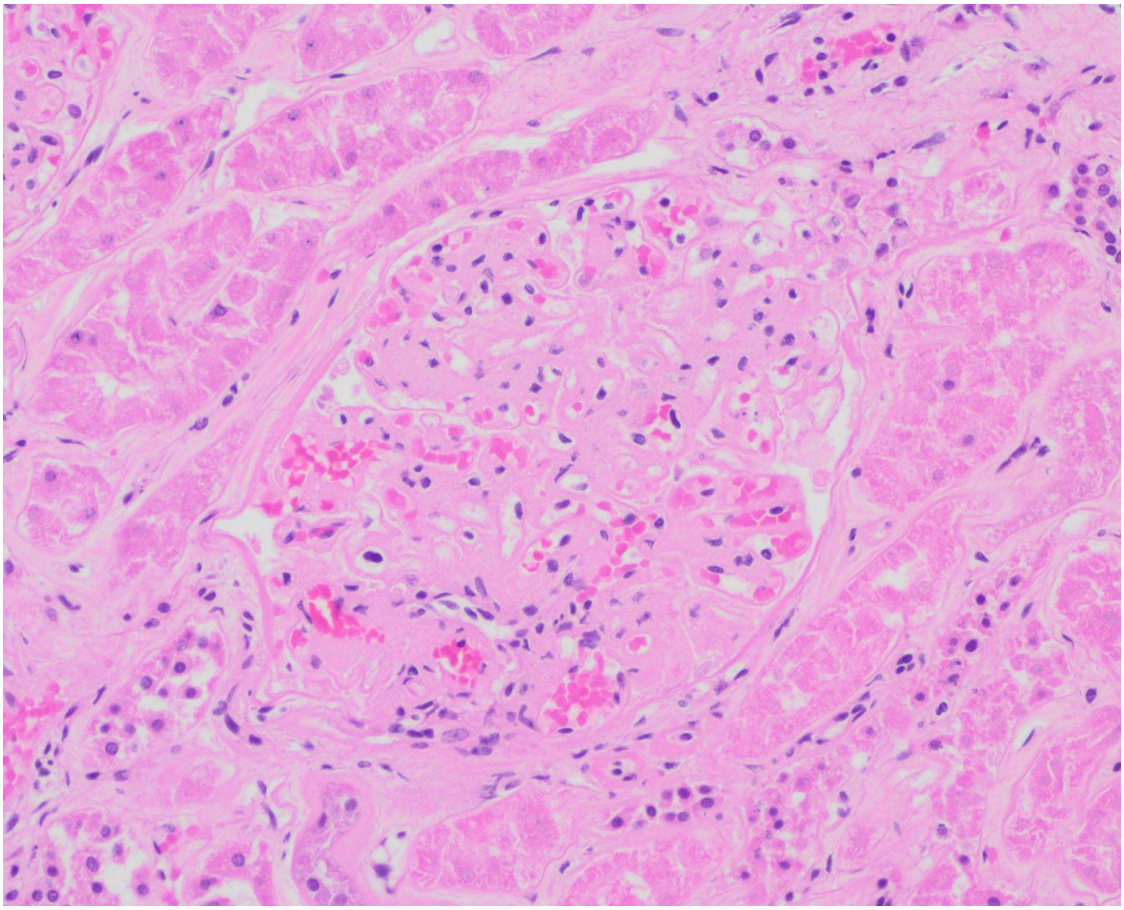


Image: Mesangial expansion in a glomerulus, H&E staining. (Image credit: Meagan Chambers/University of Washington)

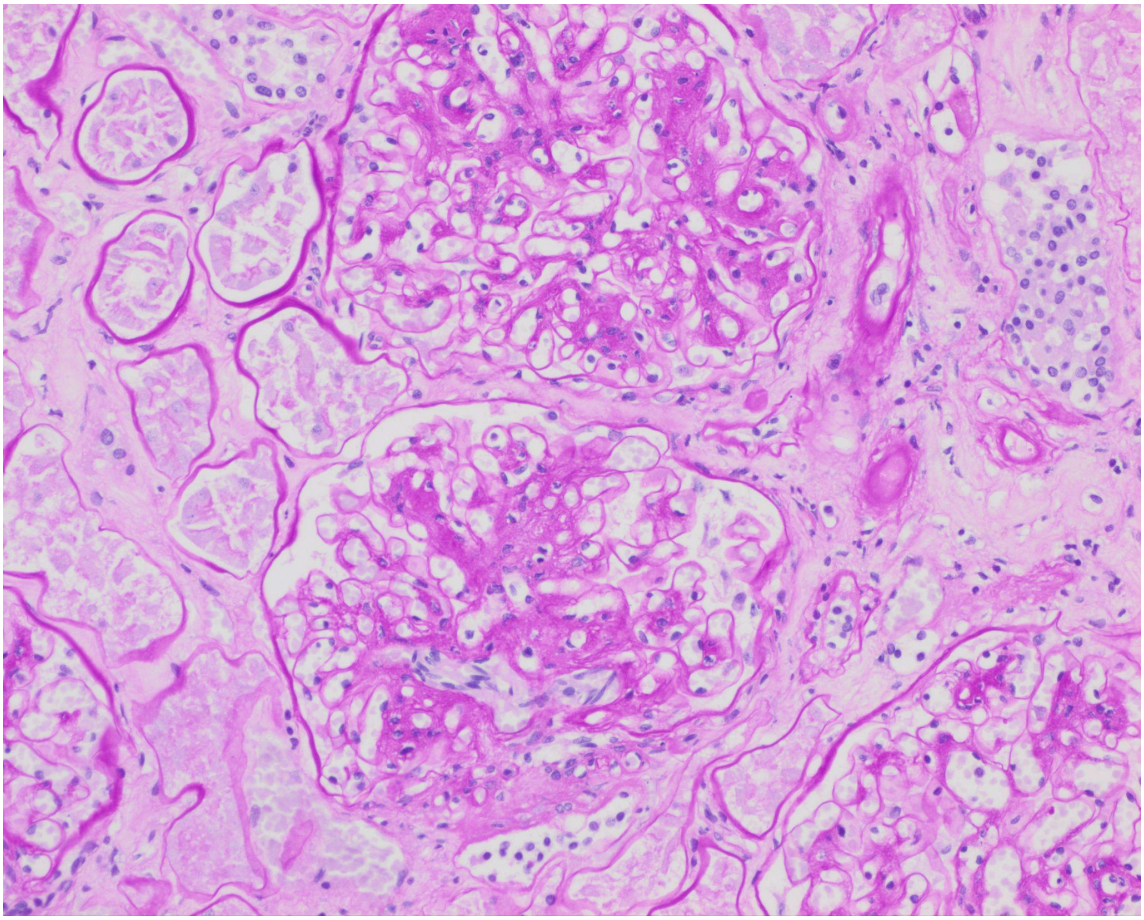


Image: Mesangial expansion in glomeruli, PAS staining. (Image credit: Meagan Chambers/University of Washington)

- In patients who clinically had severe proteinuria, tubules may show lipid droplets.
- Inflammation will often be sparse, however there may be an increase in interstitial eosinophils.
- Advanced disease includes tubular atrophy, interstitial fibrosis, and globally sclerosed glomeruli
    - Focal segmental glomerulosclerosis can also be seen in DM. (FSGS is the most common primary cause of nephrotic syndrome in the adult population and diabetes is the most common secondary cause in adults).

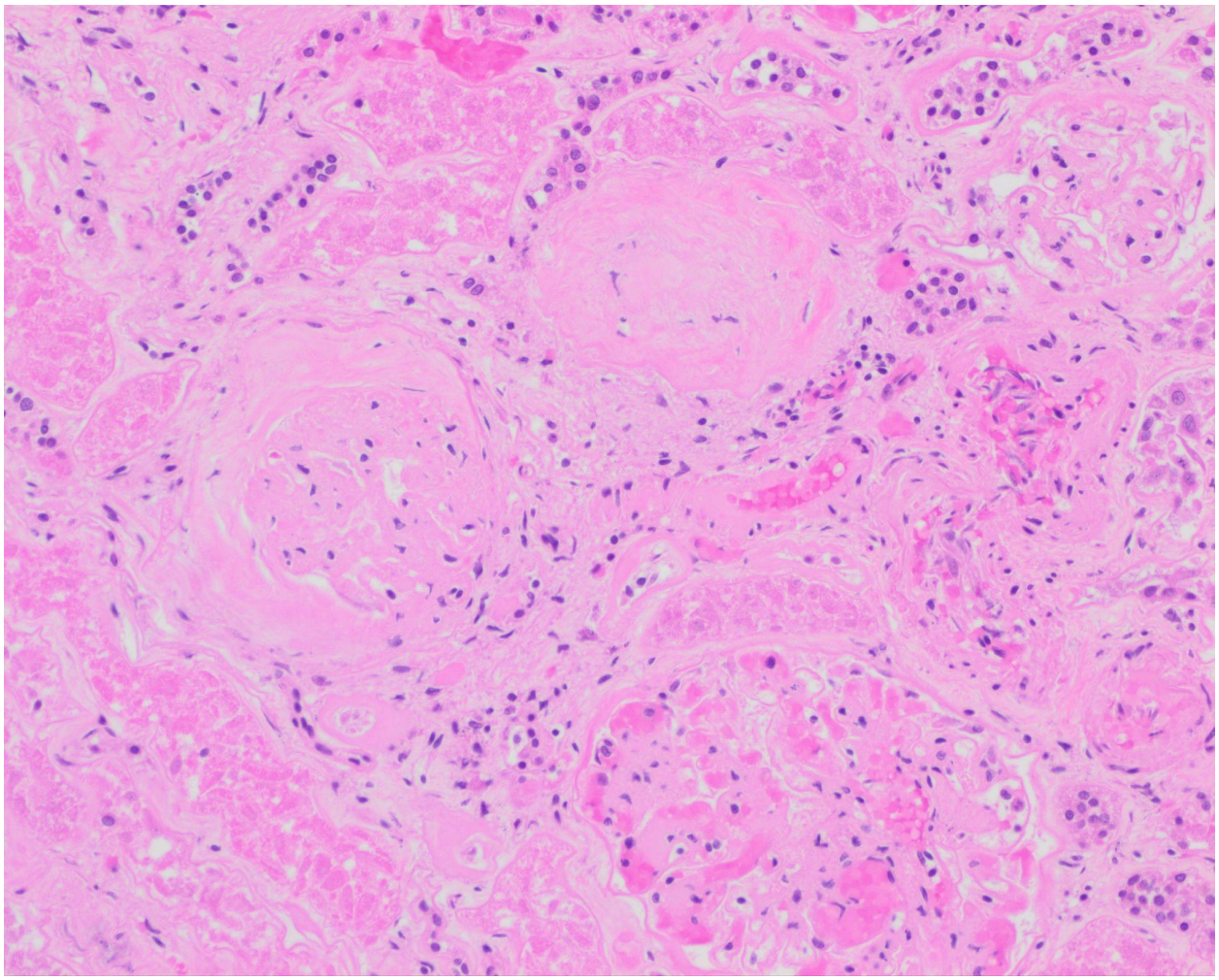


Image: Globally sclerosed glomerulus (top of the image) and a segmentally sclerosed glomerulus (middle of the image) and a non-sclerosed glomerulus with mesangial expansion (bottom of the image) all present in one high power field in a patient with DM on H&E. (Image credit: Meagan Chambers/University of Washington).

- Immunofluorescence demonstrates linear IgG and albumin in the basement membrane
- Electron microscopy demonstrates basement membrane thickening
- Patients with diabetic Ketoacidosis may demonstrate proximal convoluted tubules with subnuclear glycogen filled vacuoles (Armanni-Ebstein lesion)
- In a study by Perrone et al., medical renal diseases were classified, including diabetic nephropathy, and analyzed to see if they were noticed at the time of autopsy. They found that these diagnoses were not reported in 60% of cases during the initial autopsy evaluation. Henriksen points out that, “Since kidney biopsy is usually avoided in critically ill patients, histologic evaluation of autopsy kidneys may be the first and only opportunity to identify these diseases. This is crucial as these findings may have implications for the surviving family members, particularly for those diseases with a genetic component.” These two studies highlight the need for high quality autopsy investigation in diabetic patients.

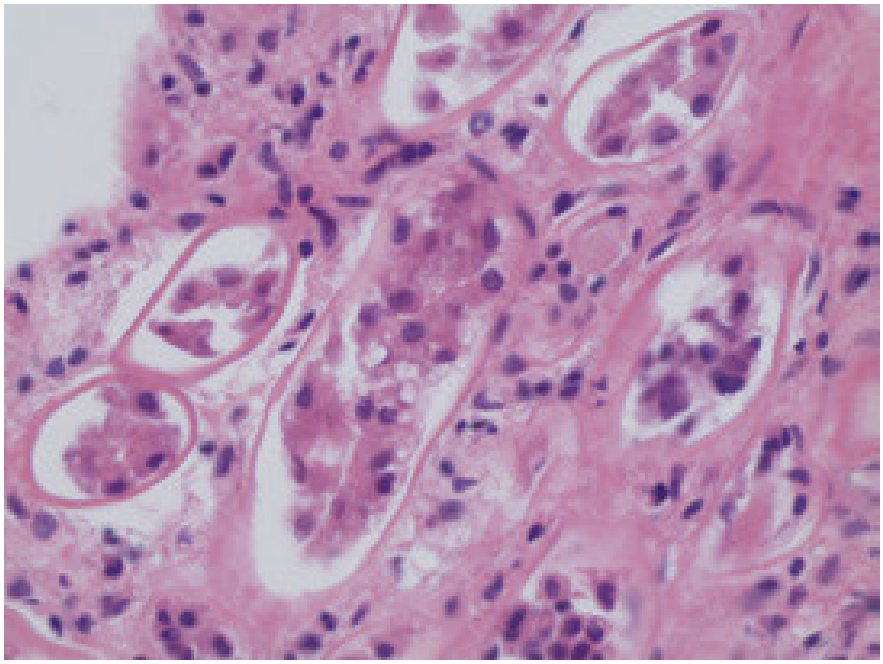


Image: Proximal convoluted tubules with subnuclear glycogen filled vacuoles demonstrating an Armanni-Ebstein lesion. (Image credit: Parai Milroy from *Academic Forensic Pathology*).

Cardiovascular

- Atherosclerosis
- Sequelae of hypertension, a common comorbidity in DM

Liver

- Glyocgenic hepatopathy can be seen in patients with poorly controlled Type I DM

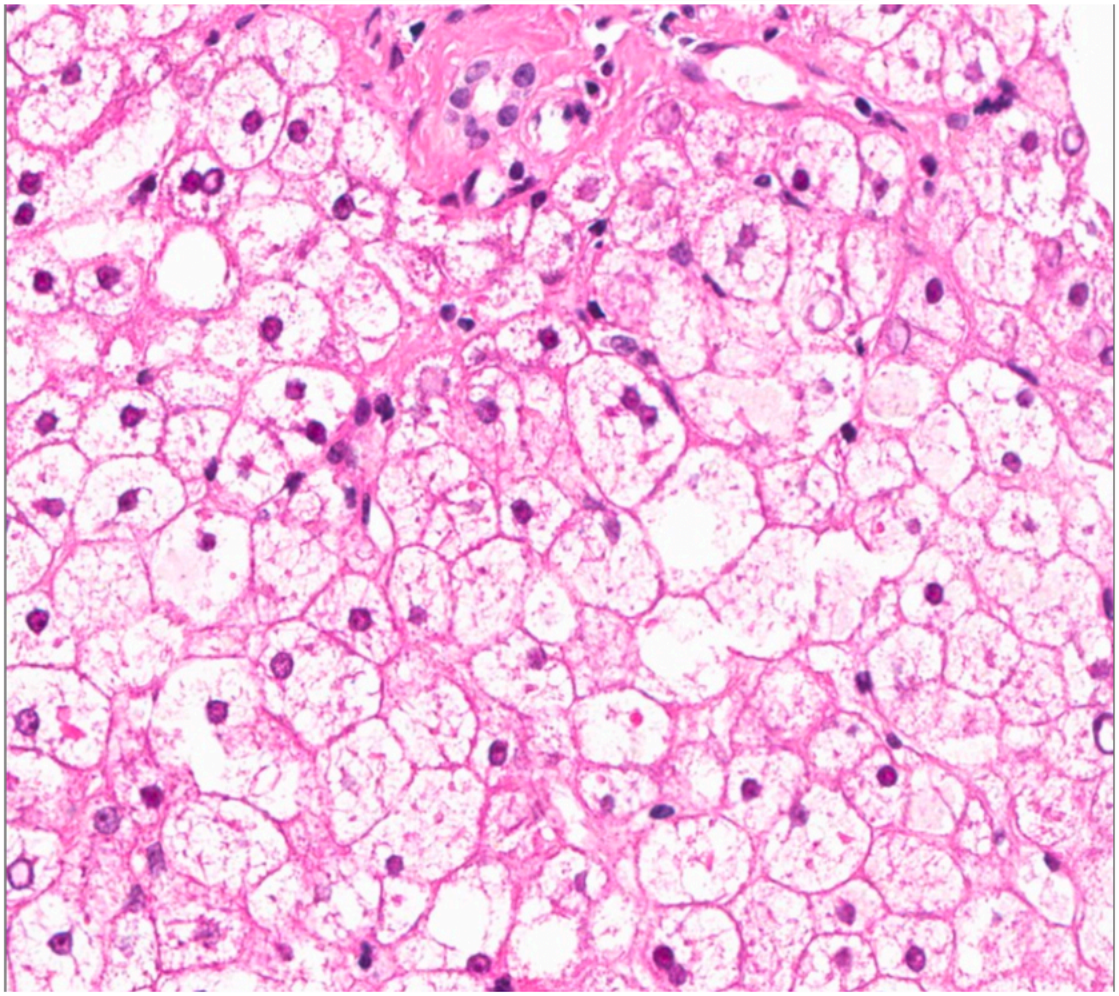
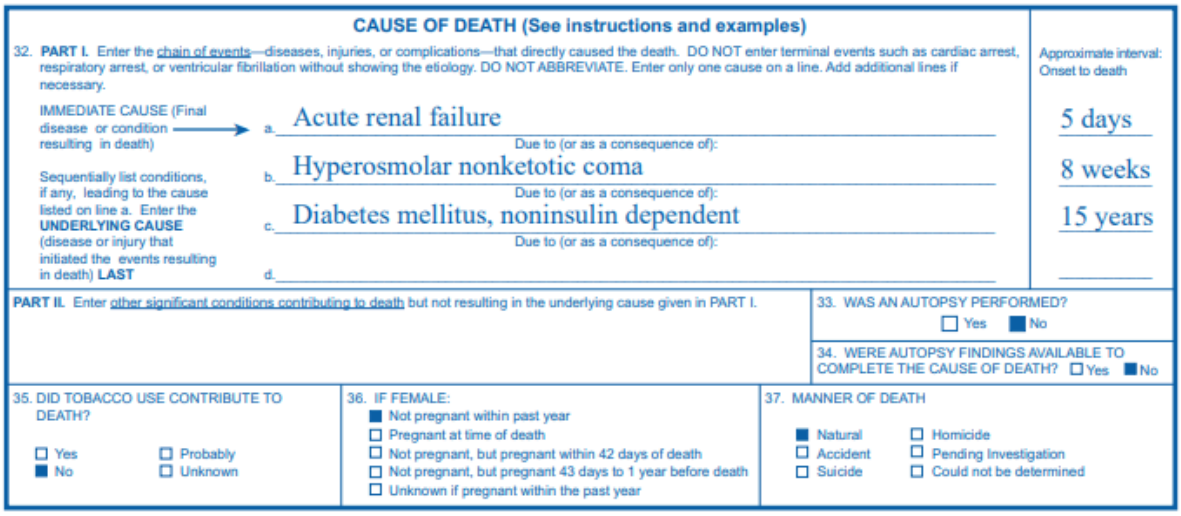


Image: Glycogenic hepatopathy. (Image credit: Maria Westerhoff, ExpertPath).

Quick Tips at Time of Reporting

Cause of death statements

- Example causes of death related to diabetes:



CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events—diseases, injuries, or complications—that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition resulting in death) → a. Acute renal failure — 5 days

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**

b. Hyperosmolar nonketotic coma — 8 weeks

Due to (or as a consequence of):

c. Diabetes mellitus, noninsulin dependent — 15 years

Due to (or as a consequence of):

d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I.

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ■ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ■ No

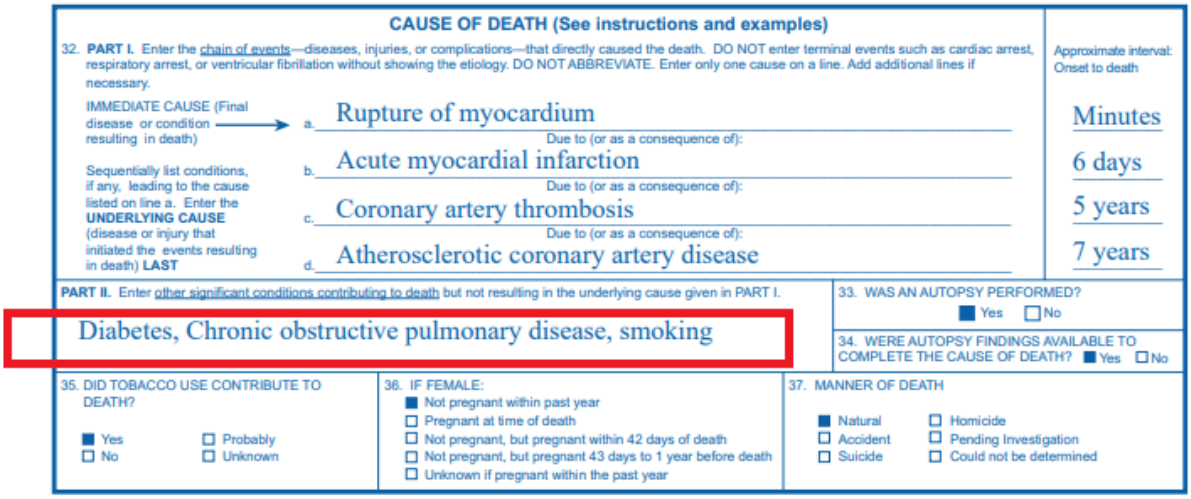
35. DID TOBACCO USE CONTRIBUTE TO DEATH? ☐ Yes ■ No ☐ Probably ☐ Unknown

36. IF FEMALE: ■ Not pregnant within past year ☐ Pregnant at time of death ☐ Not pregnant, but pregnant within 42 days of death ☐ Not pregnant, but pregnant 43 days to 1 year before death ☐ Unknown if pregnant within the past year

37. MANNER OF DEATH ■ Natural ☐ Accident ☐ Suicide ☐ Homicide ☐ Pending Investigation ☐ Could not be determined

    - Phrases like “in the setting of,” “in conjunction with” can be utilized when there are multiple events occurring.
        - Acute Myocardial Infarction in the setting of…
        - Multilobar pneumonia in conjunction with…
- Part II - Other significant contributing conditions - Diabetes should be included when appropriate - heart disease, obesity, etc

Examples of properly completed medical certifications



CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events—diseases, injuries, or complications—that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition resulting in death) → a. Rupture of myocardium — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**

b. Acute myocardial infarction — 6 days

Due to (or as a consequence of):

c. Coronary artery thrombosis — 5 years

Due to (or as a consequence of):

d. Atherosclerotic coronary artery disease — 7 years

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I.

Diabetes, Chronic obstructive pulmonary disease, smoking

33. WAS AN AUTOPSY PERFORMED? ■ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ■ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH? ■ Yes ☐ No ☐ Probably ☐ Unknown

36. IF FEMALE: ■ Not pregnant within past year ☐ Pregnant at time of death ☐ Not pregnant, but pregnant within 42 days of death ☐ Not pregnant, but pregnant 43 days to 1 year before death ☐ Unknown if pregnant within the past year

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Interpretation of ancillary testing

	DKA	HHS
Vitreous Electrolytes	WNL	Elevated Na+ secondary to dehydration
Glucose	>200	>600

Ketones	+	negative
B-Hydroxybutyrate	Positive	Negative

- Vitreous Humor Analysis
    - A vitreous glucose over 200 mg/dL is supportive of diabetes.
    - A vitreous glucose over 200 mg/dL in combination with ketoacids (beta-hydroxybutyrate and acetoacetate) is supportive of a diagnosis of diabetic ketoacidosis. pH will be consistent with metabolic acidosis.
- Serum beta-hydroxybutyrate analysis
    - Beta-hydroxybutyrate seems to be a better postmortem indicator of ketoacidosis than acetone (Palmiere 2015).
    - Decompositional changes are not associated with beta-hydroxybutyrate production and blood beta-hydroxybutyrate levels in decomposed bodies can be considered an appropriate biochemical parameter in the estimation of beta-hydroxybutyrate concentrations at the time of death (Palmiere 2015).
    - Ranges proposed by Iten and Meier:
        - up to 500 µmol/L (corresponding to 5.2 mg/dL) ⇒ normal
        - 500 to 2500 µmol/L (corresponding to 26 mg/dL) ⇒ increased
        - over 2500 µmol/L ⇒ pathological
- Serum isopropyl alcohol is a marker of ketoacidosis and a product of acetone metabolism in clinical conditions presenting with increased ketone levels.
- Serum C reactive protein is stable after death and is often increased in cases of ketoacidosis.
- Urine glucose should not be the only marker to posit a cause of death but rather can be used to confirm findings obtained from vitreous glucose and blood ketone body measurements.

Histology evaluation

- The Renal Pathology Society has classification criteria for diabetic nephropathy which can be integrated into the diagnostic line of the final autopsy report.

Class I	GBM thickening on electron microscopy; minimal, non-specific, or no changes on light microscopy
Class II	Increase in mesangial matrix
Class IIa	Mesangial expansion ≤25%
Class IIb	Mesangial expansion >25%
Class III	Nodular glomerulosclerosis; Kimmelstiel-Wilson nodules
Class IV	Advanced glomerulosclerosis; >50% glomeruli are sclerotic

(Table adapted from: Pathogenesis of Diabetic Nephropathy, Chronic Kidney Disease and Type 2 Diabetes)

- Of note, diabetes is a significant risk factor for neurodegenerative disease; neurodegenerative work up for older adults may be considered and/or indicated

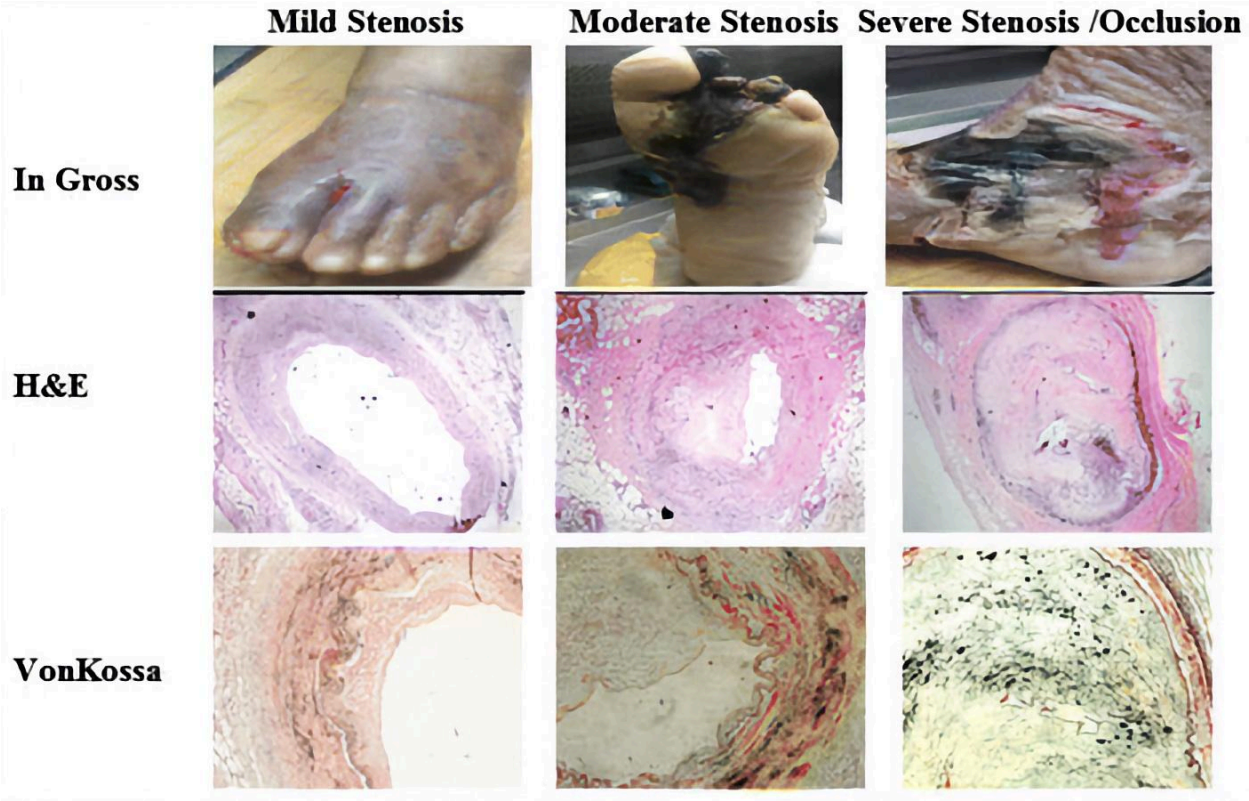

Image: Progression of atherosclerotic calcification in diabetic foot patients. (Top row) In gross observation, different degrees of gangrene, swelling, skin ulcers, and infection in diabetic foot patients among the three groups were observed. (Middle and bottom rows) Representative photomicrographs of atherosclerotic lesions in anterior tibial artery cross-sections after H&E staining (×40) and von Kossa staining (black calcium particles) (×200). (Image Credit: Wang 2016).

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