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Malakoplakia in the Urinary Bladder of 4 Puppies

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Abstract

Malakoplakia in humans most often affects the urinary bladder and is characterized by inflammation with von Hansemann–type macrophages, with or without Michaelis-Gutmann bodies, and is frequently associated with *Escherichia coli* infection. We describe the microscopic features of malakoplakia in the urinary bladder of 4 puppies. In all cases, the lamina propria of the urinary bladder was markedly expanded by sheets of large, round to polygonal macrophages with intracytoplasmic, periodic acid-Schiff-positive granules and granular inclusions, and rare Prussian blue–positive inclusions. Macrophages were positive for CD18 and Iba1. In 2 cases, Michaelis-Gutmann bodies were detected with hematoxylin and eosin stain and were best demonstrated with von Kossa stain. *E. coli* infection was confirmed in 2 cases with bacterial culture or polymerase chain reaction (PCR) and sequencing of the bacterial 16S ribosomal RNA gene. Transmission electron microscopy of one case demonstrated macrophages with abundant lysosomes, phagolysosomes, and rod-shaped bacteria. Microscopic features were similar to human cases of malakoplakia. In dogs, the light microscopic characteristics of malakoplakia closely resemble granular cell tumors and histiocytic ulcerative colitis.

Keywords

dog; granulomatous; macrophage; malakoplakia; Michaelis-Gutmann bodies; urinary bladder

Malakoplakia is a rare granulomatous disease described in humans and a few animal species including 2 pigs, 3 cats, a dog, and a macaque (Supplemental Table S1).[2,3,6,12,22,26,27] In humans, lesions are most common in the genitourinary system but can be found in many tissues including the gastrointestinal tract, central nervous system, lymph nodes, skin, breast, adrenal gland, thyroid gland, and lung.[11,25,32] Malakoplakia is often associated with debilitating diseases and/or immunosuppression such as acquired immunodeficiency syndrome, severe combined immunodeficiency, organ transplantation, tuberculosis, or

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malignancy.[5,25] Most cases occur in middle-aged women, with rare case reports in children.[5,23,24,32] The pathogenesis is unknown, but is likely associated with bacterial infection, usually *Escherichia coli*, and defective macrophage phagolysosome activity.[9,17,18]

The name malakoplakia describes the gross characteristics of the lesion (Greek: “malakos,” soft: “plakos,” plaque). The lesion may also present as single or multiple soft masses or frond-like projections.[3,25,32] Histologically, malakoplakia is characterized by sheets of large, round macrophages with prominent cytoplasmic granules and inclusions, termed von Hansemann–type macrophages.[3,25,26] These granules and inclusions are intensely periodic acid-Schiff (PAS)–positive and are ultrastructurally consistent with lysosomes and phagolysosomes, which variably contain bacteria and bacterial breakdown products. Intracellular and extracellular Michaelis-Gutmann (MG) bodies develop with chronicity, and likely represent the accumulation of mineralized bacterial breakdown products.[17–19,25] MG bodies are targetoid lesions composed of iron and calcium and, although not present in all cases, are pathognomonic for malakoplakia.[9,32] The objective of this study was to describe cases of malakoplakia in the urinary bladder of puppies.

Materials and Methods

Malakoplakia was diagnosed in the urinary bladder of 4 puppies based on similarity to the above-mentioned microscopic features of the human disease. Cases 1 and 2 were diagnosed at the Animal Disease Diagnostic Laboratory at Purdue University, and cases 3 and 4 were diagnosed at Antech Diagnostics. All available information including signalment, history, clinical findings, and histopathologic findings were compiled from medical records.

Diagnosis of malakoplakia was confirmed via characteristic microscopic lesions, histochemistry, and immunohistochemistry (IHC) for CD18 and Iba1. Tissue samples obtained at autopsy or surgical biopsy were fixed in 10% neutral-buffered formalin, embedded in paraffin, and 3-μm thick sections were stained with hematoxylin and eosin (HE), PAS, von Kossa, Prussian blue, Giemsa, Brown and Hopps (except case 2), Grocott’s methenamine silver (GMS), and Ziehl-Neelsen stain. For IHC for CD18, sections of urinary bladder were incubated with the primary antibody (clone CA16:3C10, Dr P. F. Moore, Davis, CA) at room temperature for 60 minutes at 1:100 dilution, heat-induced antigen retrieval (HIER) with citrate buffer, and labeled with EnVision plus (Dako); dog lymphoid tissue was used as the positive control. For IHC for Iba1, the primary antibody (Biocare Medical) was incubated at room temperature for 60 minutes at 1:400 dilution, HIER with Diva buffer (Biocare Medical), and detected with a rabbit polymer (Biocare Medical); dog brain was used as the positive control.

For transmission electron microscopy (TEM) of case 1, formalin-fixed urinary bladder was further fixed in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, and postfixed in 1% osmium tetroxide containing 0.8% potassium ferricyanide. The tissue was dehydrated with a graded series of ethanol, transferred into acetonitrile, and embedded in EMbed-812 resin. Sections were cut on a Reichert-Jung Ultracut E ultramicrotome and stained with 4% uranyl acetate and lead citrate. Digital images were acquired on a FEI tecnai T12 electron microscope equipped with a tungsten source and operating at 80 kV.

A portion of the 16S rRNA gene was amplified from formalin-fixed, paraffin-embedded tissue scrolls using primer pair S-D-Bact-0341-b-S-17/S-D-Bact-0785-a-A-21.[15] Briefly, paraffin was removed using xylene and an ethanol wash. The nucleic acid was extracted with the MagMAX CORE Nucleic Acid Purification Kit (ThermoFisher Scientific). Amplification of a product was verified by gel electrophoresis. The polymerase chain reaction (PCR) product was purified using the Pure-Link PCR Micro kit (ThermoFisher Scientific), and Sanger sequencing was performed, using both the forward and reverse primers (Eurofins Genomics). The forward and reverse sequences were evaluated and aligned using Geneious Prime (https://www.geneious.com/). The identity of the bacterial product was determined by an NCBI blastn search (megablast) of the consensus sequence using both the 16S ribosomal RNA sequences database and the nucleotide collection (nr/nt) database. Species identification required >99% sequence similarity.

Results

Case 1 was a 6-week-old female Pug puppy with a history of straining to urinate and failure to thrive. Case 2 was a 4.5-month-old female English bulldog with a history of urinary incontinence since birth. Case 3 was a 7-month-old spayed female bulldog (exact breed not specified) with a history of chronic urinary tract infections beginning at 8-weeks-old. Case 4 was an 8-month-old female English bulldog with a history of chronic urinary tract infections.

Case 1 was euthanized and submitted for a full autopsy. Grossly, the mucosa of the urinary bladder was diffusely and markedly thickened by nodular masses (Fig. 1). Biopsy samples of the urinary bladder were submitted for cases 2 to 4. Reportedly, the urinary bladder mucosa of cases 2 to 4 was thickened by nodular or frond-like masses. A urinary diverticulum was reported in cases 2 and 3. A urine culture collected at the time of presentation of case 2 yielded *E. coli*.

Microscopic findings in all 4 cases were similar. In HE-stained sections, the lamina propria of the urinary bladder was markedly expanded by sheets of macrophages (Fig. 2). Macrophages were round to polygonal with abundant cytoplasm, which contained fine to coarse eosinophilic granules and eosinophilic granular inclusions up to 12-μm-diameter that variably displaced the nucleus to the periphery (Fig. 3). Mild-to-moderate numbers of macrophages also extended into the inner tunica muscularis. The lamina propria of at least one distal ureter in case 1 was also expanded by large numbers of macrophages (ureters were not available in the other cases). Multinucleated macrophages were not present. Scattered between the macrophages were small numbers of lymphocytes, plasma cells, and neutrophils. Multifocal lymphoid nodules were in the lamina propria of cases 1 and 4. The urothelium was diffusely ulcerated in case 4. In the other cases, the urothelium was hyperplastic with multifocal regions of erosion and/or ulceration, and contained scattered macrophage infiltrates.

Macrophages had diffuse, strong, cytoplasmic, and membranous positive staining for Iba-1 and CD18 with immunohistochemistry (Figs. 4, 5). Other leukocytes were also positive for CD18. Cytoplasmic granules and inclusions were intensely PAS-positive (Fig. 6) and

moderately argyrophilic with GMS. With Giemsa, myriads of rod-shaped bacteria were within the cytoplasm of numerous macrophages in cases 1 and 2 (Fig. 7). All cases were negative for gram-positive bacteria with Brown and Hopps, acid-fast bacteria with Ziehl-Neelsen, and argyrophilic organisms with GMS.

Michaelis-Gutmann bodies were observed in cases 3 and 4. With HE, MG bodies were rare, cytoplasmic or extracellular, most often within the deep lamina propria or inner tunica muscularis, and round to oval with a targetoid pattern of alternating regions which were darkly basophilic and lightly basophilic to clear (Fig. 8). The cytoplasmic inclusions in macrophages ranged from eosinophilic to lightly basophilic (consistent with mineral). With von Kossa, many inclusions and targetoid MG bodies were positive throughout the lamina propria, mostly within macrophages (Fig. 9). Cases 1 and 2 were negative with von Kossa. Rare cytoplasmic Prussian blue–positive inclusions were within macrophages of all 4 cases (Fig. 10).

Urinary bladder from case 1 was available for TEM. The cytoplasm of macrophages diffusely contained large numbers of lysosomes and phagolysosomes. Many phagolysosomes contained rod-shaped bacteria (Fig. 11). Some macrophages were degenerate and filled with cytoplasmic rod-shaped bacteria. MG bodies were not observed.

PCR and sequencing of the bacterial 16S ribosomal RNA gene yielded *E. coli* in urinary bladder formalin-fixed, paraffin-embedded tissues from case 1. Cases 2 to 4 yielded unidentified sequences.

Discussion

The pathologic findings in these canine cases of malakoplakia share many features of malakoplakia in humans including gross findings, light microscopic findings, tissue distribution, TEM findings, and the presence or history of bacterial infection. The similarities between human and canine cases of malakoplakia suggest a common pathogenesis; however, some differences deserve recognition.

In all cases, the gross lesions were typified by marked thickening of the mucosa by nodular or frond-like projections. Similar descriptions are reported in the human literature; however, most lesions in humans are described as soft yellow to brown plaques with central umbilication.[9,11,25] Yellow to brown discoloration and/or umbilication of the lesions was not appreciated in any of the 4 puppies of the current report; however, these gross changes may have gone unnoticed by the veterinarians who submitted biopsies from cases 2 to 4. Microscopically, marked infiltration of the affected tissue by large, round to polygonal macrophages with PAS-positive granules and inclusions is characteristic of malakoplakia.[25] Light microscopy findings were strikingly similar between the 4 puppies and were consistent with human cases of malakoplakia.

Cases 3 and 4 demonstrated MG bodies, which are pathognomonic of malakoplakia. MG bodies were first characterized in human cases, and are described as basophilic, intracellular or extracellular, targetoid structures. MG bodies are reportedly composed of calcium, organic components, and iron; therefore, von Kossa and Prussian blue are

frequently employed to better visualize MG bodies.[9,25,32] In our study, MG bodies were rarely identified with HE in cases 3 and 4; however, von Kossa stain revealed many more targetoid MG bodies. Von Kossa stain also highlighted many mineralized inclusions in macrophages, likely representing immature MG bodies. Immature MG bodies are described in TEM studies as mineralized concretions that do not yet have a targetoid appearance.[17,18] Cases 1 and 2 lacked MG bodies with HE, and macrophage inclusions were negative with von Kossa stain. These cases might have been more acute; MG bodies are described only in the chronic phase of malakoplakia in people.[8,25] In addition, these puppies were younger: case 1 was 6 weeks old, and case 2 was 4.5 months old, compared to cases 3 and 4, which were 7 and 8 months old, respectively.

Although MG bodies reportedly contain iron, MG bodies in cases 3 and 4 were rarely positive with Prussian blue stain, and cases 1 and 2, which lacked MG bodies with von Kossa or HE, contained rare Prussian blue–positive inclusions. This is contrary to many other reports in humans, which demonstrate MG bodies to be Prussian blue–positive.[25] Prussian blue staining characteristics are inconsistently reported in the few animal reports of malakoplakia.[2,3,6,12,22,26,27] MG bodies are hypothesized to develop from defective phagolysosome function and the accumulation of bacterial breakdown products.[17–19] Inherent differences in iron metabolism between different species of bacteria and animals and variation in antimicrobial defenses (such as iron sequestration) might result in variation in MG iron content.[21] In the one other report of malakoplakia in a dog, Prussian blue staining was not performed.[3]

The pathogenesis of malakoplakia is not well defined. An inherent defect in macrophage phagolysosome activity is supported by TEM studies in humans, which demonstrate macrophages distended with lysosomes and large phagolysosomes.[17–19] A similar pathogenesis is suspected in animals, and is supported by our ultrastructural findings in case 1 and the young age of the puppies in our study. Lesions were not reported in any other tissue in cases 2 to 4, and granulomatous inflammation was absent from all other examined tissues in case 1. If macrophages are inherently defective, lesions might be expected in other tissues; however, malakoplakia is typically only reported in one or a few tissues in human cases.[25,32] This tissue distribution may be due to the hypothesized requirement of bacterial infection in initiating malakoplakia lesions.[9,32] Microscopically, a myriad of cytoplasmic rod-shaped bacteria were in many macrophages in cases 1 and 2. *E. coli* was detected via PCR and sequencing for case 1, and urinary culture for case 2. Rod-shaped bacteria were not visible with light microscopy in cases 3 and 4; however, these cases had a reported history of chronic urinary tract infections. In human cases, bacteria are not always distinguishable microscopically; however, bacterial fragments are usually demonstrated ultrastructurally.[9,17,18] *E. coli* is the most common isolate in human cases. Other common isolates include *Mycobacterium tuberculosis, Proteus spp., and Staphylococcus aureus*.[32]

Malakoplakia most commonly affects the urinary bladder of adult, female humans who are immunocompromised or have a debilitating disease.[4,9,16,32] Reports in children or otherwise healthy individuals are rare.[5,14,23,24] All 4 cases of the current report occurred in female puppies and the only other report of malakoplakia in dogs also occurred in a female puppy. In that report, the puppy was a Staffordshire bull terrier puppy with a history of chronic *E.*

coli cystitis.[3] Chronic bacterial infection is implicated in the pathogenesis of malakoplakia, and since the female dog is more prone to urinary tract infections than the male, it is not surprising that all reported cases to date are female.[7] A urinary diverticulum was clinically suspected in cases 2 and 3 and may have served as a nidus for chronic bacterial infection. Clinical suspicion of immunosuppression, history of immunosuppressive therapy, or history of debilitating disease was not reported in any of the cases. After complete autopsy, case 1 was diagnosed with sepsis with *E. coli* and *Streptococcus canis*, and collagen type III glomerulopathy (previously reported as case 1 in Davis et al[10]). Collagen type III glomerulopathy results in proteinuria and eventual renal failure.[1] Clinical data were not available for this case; however, this debilitating comorbidity may have predisposed this puppy to malakoplakia in the urinary bladder.

Malakoplakia is reminiscent of canine histiocytic ulcerative colitis (HUC). Both malakoplakia and HUC are commonly associated with *E. coli* infection and are characterized by marked infiltration of the affected tissues by PAS-positive macrophages.[9,28] All 4 puppies of this report also had mucosal ulceration, similar to HUC. In TEM studies of HUC, macrophages contain many lysosomes and phagolysosomes, similar to malakoplakia.[13,16,29] HUC, however, lacks MG bodies.[27] The gross appearance of these 2 lesions usually differs in that malakoplakia tends to form nodules, polyps, and plaques as compared to the diffuse thickening of HUC.[14,28,31,32] However, diffuse thickening of the colon has been reported with malakoplakia.[30] The gastrointestinal tract is the second most common location of malakoplakia in humans.[14,32] To date, malakoplakia has not been diagnosed in the gastrointestinal tract of animals. Acute cases of malakoplakia, which lack MG bodies, may be indistinguishable from HUC. The pathogenesis for malakoplakia and HUC is not understood. More studies are needed to elucidate the subtle differences between these 2 diseases, which may represent different morphologic manifestations of a similar defect in pathogen clearance. Screening of HUC cases for MG bodies with von Kossa stain may help determine if these represent the same disease process.

In this article, the term von Hansemann cell was avoided when describing the macrophages in malakoplakia of animals. Although the term von Hansemann cell is used exclusively in malakoplakia in the human literature, the morphologic features of von Hansemann cells are shared with macrophages of other disease processes such as HUC and histiocytic storage disease in animals.

Pathologists may misinterpret malakoplakia masses, which are composed of a homogenous population of large, round to polygonal cells with granular cytoplasm, as neoplastic. In fact, case 4 was initially diagnosed as a granular cell tumor prior to the application of immunohistochemistry markers for macrophages. Similar to malakoplakia, granular cell tumors typically consist of a homogenous population of round to polygonal cells with abundant, granular cytoplasm, minimal cellular atypia, and PAS-positive granules. Though granular cell tumors have defined sites of predilection, both malakoplakia and granular cell tumors may be diagnosed in any tissue.[20,32] Therefore, we recommend that malakoplakia be considered a differential for granular cell tumors.

In conclusion, we describe malakoplakia in the urinary bladder of 4 puppies. Lesions were characterized by marked expansion of the lamina propria by sheets of large, round to polygonal macrophages with intracytoplasmic PAS-positive granules and inclusions, with or without MG bodies. Von Kossa best highlighted MG bodies. Two cases were diagnosed with *E. coli* infection, which is a common isolate in human cases of malakoplakia. Differential diagnoses for malakoplakia include HUC or granular cell tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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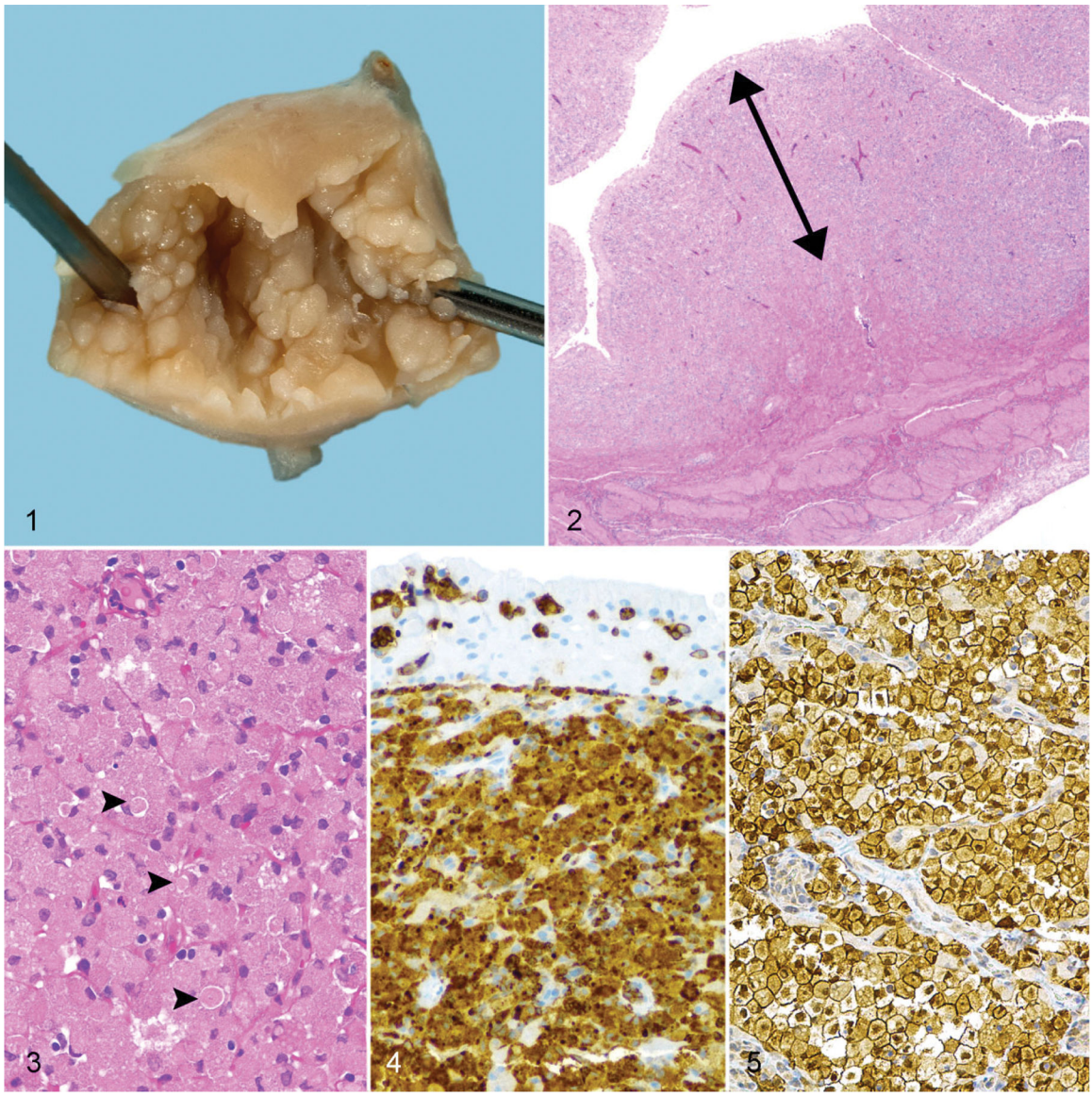
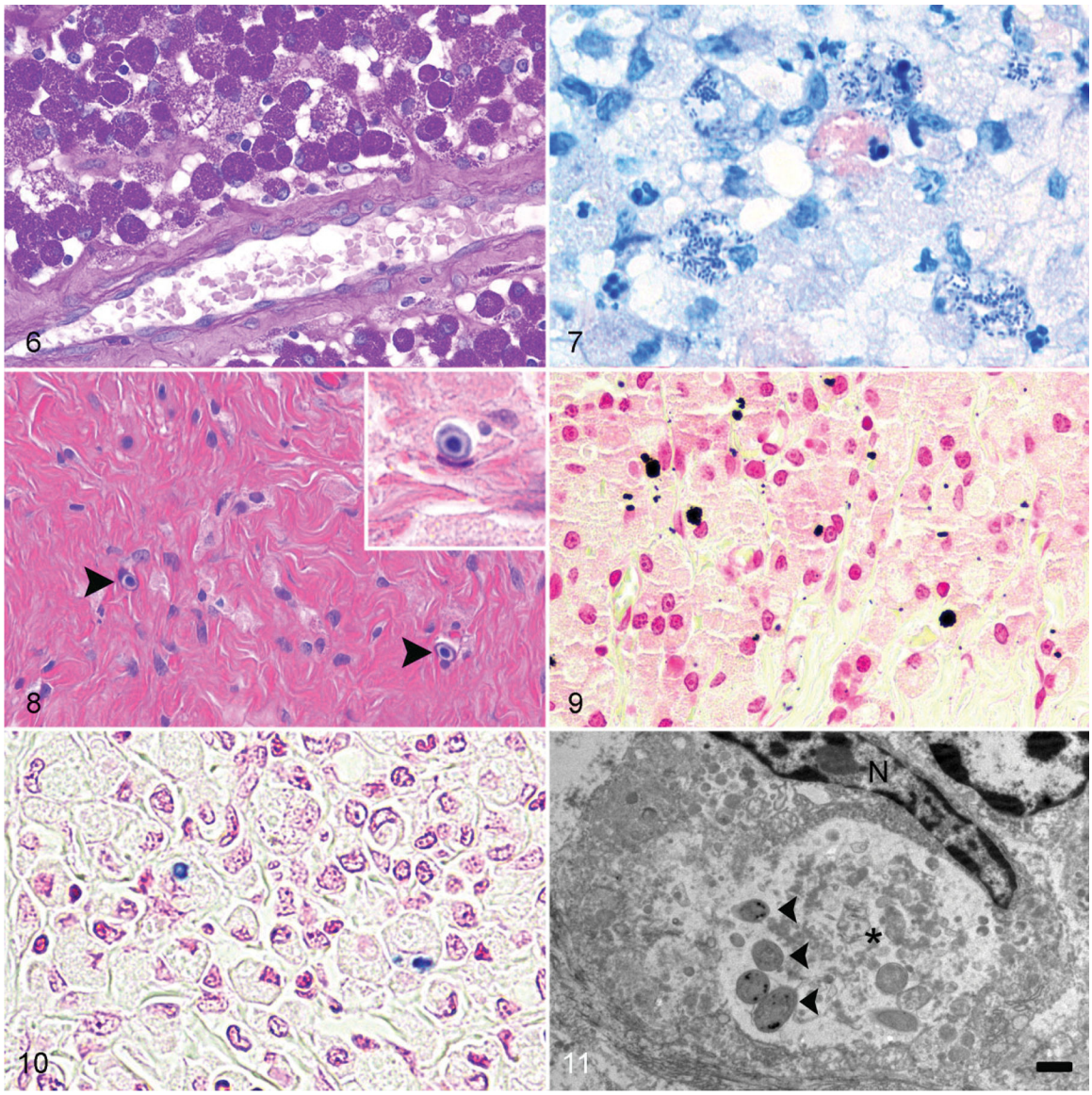


Figures 1–5.

Malakoplakia, urinary bladder, dogs. **Figure 1.** Case 1, formalin-fixed. The mucosa is markedly thickened and has a nodular surface. **Figure 2.** Case 1. The lamina propria (double arrow) is markedly expanded by cellular infiltrates. The urothelium is mildly hyperplastic. Hematoxylin and eosin (HE). **Figure 3.** Case 3. The cellular infiltrate consists of sheets of large, round to polygonal macrophages with abundant eosinophilic granular cytoplasm and round eosinophilic granular inclusions (arrowheads). HE. **Figure 4**. Case 2. Macrophages and mixed leukocytes express CD18. Scattered leukocytes infiltrate between urothelial cells. Immunohistochemistry (IHC) for CD18. **Figure 5**. Case 2. Macrophages express Iba1. IHC for Iba1.



Figures 6–11.

Malakoplakia, urinary bladder, dogs. **Figure 6.** Case 3. Macrophage cytoplasmic granules and inclusions are intensely periodic-acid Schiff (PAS)–positive. PAS. **Figure 7.** Case 2. Multiple macrophages contain dark blue cytoplasmic rod-shaped bacteria. Giemsa**. Figure 8**. Case 4. Within the inner tunica muscularis are multiple Michaelis-Gutmann (MG) bodies (arrowheads). Inset: A MG body is in the cytoplasm of a macrophage. HE. **Figure 9**. Case 4. Macrophages contain numerous black-staining cytoplasmic inclusions (mineral). Von Kossa. **Figure 10**. Case 1. Macrophages contain rare blue cytoplasmic inclusions. Prussian blue. **Figure 11**. Case 1. A macrophage has a large phagolysosome (asterisk) containing multiple rod-shaped bacteria (arrowheads). The nucleus (N) is peripheralized. Bar = 1 μm. Transmission electron microscopy