Chapter 15

The Urinary System

C R Huxtable

Introduction

Aims and scope of the presentation

With these notes and an accompanying powerpoint slide show, we will review some pathological states of the ruminant urinary tract. The focus will be on the most common conditions and the gross anatomical changes associated with them. The emphasis as far as practicable, will be on FIRST making an assessment of the basic nature of any disease process thought to be present, before SECOND, listing possible aetiologies.

In terms of frequency of occurrence there is little doubt that the most significant urological problem across the ruminant species is urethral obstruction, with nephrotoxic injury likely to run second. Primary nephritis is generally of sporadic occurrence as is primary urinary tract neoplasia, apart from that associated with exposure to bracken fern. Also sporadic are renal amyloidosis (included) and developmental anomalies (not included)

In terms of making **gross** diagnoses of renal disease, it is frequently not possible to be highly specific. Oftentimes, renal lesions are merely part of a multisystem disease (e.g. malignant catharral fever, lymphoma), or simply reflect severe disease in another system (e.g. haemolysis,myolysis, hepatic disease, enterotoxaemia). Regardless of aetiology, **acutely** damaged or inflamed kidneys tend to be symmetrically swollen and either pale mottled or dark mottled. **Chronically** damaged or inflamed kidneys may also be greatly enlarged, but variably distorted by fibrosis, or they may be pale, contracted and toughened by fibrosis. There is thus no shame in making an initial diagnosis of "acute" or "chronic nephropathy" and in the absence of additional gross clues, leaving further refinement of the diagnosis to the microscope or lab test

In the lower urinary tract the detection of uroliths and associated pathologies is generally fairly straightforward, as is the differentiation of acute versus chronic injury to the mucosa of the bladder. The major intellectual exercise involves identifying predisposing and underlying causes.

Since the theme of this meeting is gross pathology, no reference list or bibliography is provided, as the basic information is readily available in standard texts However, a list of websites for visual material will be made available at the meeting.

Obstructive Urolithiasis

General

Although macro-uroliths can form and grow in the renal pelvis as well as in the bladder, they seldom obstruct the renal pelvis or ureters. Urethral obstruction however, is possibly the most common fatal affliction of the male urinary tract in all ruminant species. The various structural peculiarities of the ruminant penis provide ample opportunity for urethral obstruction and the predilection sites are well known. In addition, castrated animals are at higher risk due to suppressed development of the penis and urethra. The pathogenesis of urolithiasis is complex and beyond the scope of this presentation. Suffice it to say that diet, body water balance, urine flow and infection have been implicated to varying degrees in relation to different types of uroliths. The major culprits in ruminants are struvite, silica, carbonates, oxalate, and "Clover stones" in sheep. According to the chemical nature of the precipitated material, the obstructing mass can be a hard "stone", or a plug of fine crystalline or soft sludge. As well as causing the problem of urine retention, obstructions promote bacterial growth in the stagnant urine, a significant factor in many cases.

Location and character of lesions

The common sites of obstruction in the **penile urethra** are the ischial arch, and the sigmoid flexure. Lodgement of a hard stone will generally cause ulceration at the site; acute secondary bacterial infection will frequently occur, sometimes ascending to the bladder. Ulceration and acute urethritis predispose to urethral rupture, and the leaking urine will track into the subcutis of the prepuce and perineal area, leading significant oedematous swelling. The presence of infection and the irritant nature of the urine rapidly cause acute cellulitis, a major factor in fatal outcomes. In these situations rupture of the bladder is not common, and there is insufficient time for hydronephrosis to develop (see below). However, in occasional cases circulatory compromise in the kidneys can lead to quite massive intra- and peri-renal haemorrhage.

In sheep, obstruction of the **vermiform appendage** may allow the penile urethra to remain intact, thus placing maximum pressure stress on the bladder. Over-distension of the bladder compromises blood flow within its wall, leading to oedema, degeneration and after several days eventual rupture, usually at the vertex. By this time some dilation of the renal pelvis and calyces may also be evident.

Hydronephrosis

General

Hydronephrosis is the anatomical alteration of the kidney(s) that results when there is continued glomerular filtration in the face of significant obstruction of the free-flow of urine from the renal pelvis. Thus it can be unilateral or bilateral and its severity depends upon the degree and acuteness of obstruction, which might occur anywhere from the proximal

ureter to the urethra. Obstructing lesions may be external and compressive, intramural, or intraluminal, and be due to malformations as well as acquired lesions. Hydronephrosis can be a congenital condition.

Initially, the pelvis and calyces expand, the renal medullary tissue regresses, and in the most severe case there is progressive transformation of the affected kidney to a urine-filled cyst with a rim of cortical tissue. Regression of renal tissue is due both to apoptosis and to ischemic necrosis brought about by vascular compromise. **Partial** or **intermittent** rather than complete obstruction to urine flow provides the most potential for a severe lesion since this allows glomerular filtration to continue over a long period even as renal tissue disappears.

Character of the lesion under various circumstances

Some generalizations can be made on the effects of different sites and degrees of obstruction.

Long term partial/intermittent **urethral** obstruction (an uncommon event), would be expected to cause bilateral hydro-ureter and moderate bilateral hydronephrosis. **Acute complete** urethral obstruction (a common event) causes death before there is much opportunity for hydronephrosis to develop. Generally the kidneys are swollen and the pelvis and calyces dilated but not enlarged. Occasionally massive intra- and peri-renal haemorrhage can occur.

Long term, unilateral, partial/intermittent **ureteral** obstruction would have the potential to cause the maximum degree of hydronephrosis on the affected side, together with compensatory hypertrophy of the unaffected kidney. Alterations in the affected ureter would depend upon the nature and site of the obstruction. Acute, complete, unilateral ureteral obstruction might produce a moderate degree of hydronephrosis before renal circulation would shut down, glomerular filtration would cease and renal atrophy would follow.

Patterns of Cystitis

General

Cystitis is mostly caused by bacterial infection derived from the rectal/perineal flora, and predisposed to by urinary stasis/stagnation and/or mucosal trauma induced by such things as catheterization or uroliths. Sometimes it stems from associated genital tract infections. There is a fairly constant threat of bacterial infection even in the absence of urolithiasis, and any animal subject to urinary stasis/stagnation of whatever cause is at risk.

In **acute** cystitis reactions, the characteristic appearance of the lesion (see below) will make a morphologic diagnosis relatively straightforward. A specific diagnosis will depend on the identification of associated lesions or underlying predisposing causes. As mentioned in the preceding segment, severe acute bacterial cystitis is a frequent complication of urethral obstruction by uroliths in cattle. Apart from bacterial infections,

acute cystitis is often a major gross lesion of Malignant Catharral Fever in cattle and deer, and in some instances it may be caused by the presence of an irritant or toxin in the urine (as exemplified by cyclophosphamide in small animals or blister beetle toxin in herbivores in the U.S.). This is a possibility to keep in mind in cases where no other obvious cause can be identified.

Occasionally an acute change known as **"emphysematous cystitis"** will be encountered, in which the mucosa is transformed by the accumulation of interstitial gas bubbles. This is generally taken to indicate glucosuria and subsequent bacterial fermentation. In ruminants it has been recorded in animals receiving intravenous dextrose medication, and sometimes in enterotoxaemia.

In **chronic** cystitis reactions the gross pathology is dominated by the effects of hyperplastic changes in the mucosa and the massive accumulation of inflammatory cells within and beneath it. The least intense reactions occur in response to mechanical irritation by vesical calculi, while more intense reactions reflect chronic infection.

Distribution and character of lesions

In **acute bacterial cystitis** there is usually a diffuse lesion in which the mucosa is swollen and hyperaemic over its entire surface, and the bladder content sanguinous or even containing blood clots. In lesions of greatest severity, fibrino-necrotic changes can produce a dirty, yellowish adherent sheet over the mucosal surface. In **Malignant Catarrhal Fever** mucosal hyperaemia may be patchy and submucosal haemorrhage is localized and variably extensive.

In **chronic cystitis** the entire mucosal surface may be irregularly reddened, thickened, folded, and in greatest severity, polypoid. Individual polyps may break down and haemorrhage focally, or undergo cystic mucoid degeneration. Occasionally the formation of myriad aggregations of lymphocytes under the mucosa gives rise to a **follicular** pattern of chronic cystitis, in which the surface is covered with small grayish nodules.

Bracken Fern and Bladder Lesions

General

The clinical state of enzootic haematuria in cattle, and occasionally sheep, is highly associated with chronic exposure to strains of bracken (*Pteridium sp.*) and perhaps other ferns, producing a range of toxins and carcinogens (notably ptaquiloside). A bovine papilloma virus may also play a role. A spectrum of proliferative lesions can develop in the bladder, beginning with mucosal angiomatous, fibromatous and papillomatous tumours, but progressing to malignancies such transitional or squamous cell carcinoma, haemangiosarcoma, fibrosarcoma or leiomyosarcoma, often in combination.

Distribution and character of lesions

The changes tend to be patchy rather than diffuse, but may be extensive and confluent. When benign they are expected to be confined to the mucosal surface and may be in multinodular clusters. When malignant they are expected to be extensively ulcerated and more deeply penetrating, and metastatic deposits may occur in iliac lymph nodes and in advanced cases, in the lungs.

Acute Nephrotoxicity

General

Nephrotoxicity is a reasonably frequent event in our part of the world, usually arising from plant toxins, and usually manifesting as an acute and often fatal episode. Occasionally the toxin is a drug, or environmental chemical. The prime target for chemical nephrotoxins is the proximal tubular epithelium, and the classical response is acute necrosis of these cells with shedding of necrotic debris into the tubule lumens (acute tubular necrosis or ATN), leakage of filtrate from the damaged tubules, and reflex changes in renal blood flow (because these tubular changes predispose to massive wasting of sodium due to failure of resorption, there is a rapid vascular response to minimize glomerular filtration by shutting down blood flow). In general, an animal with acute renal failure resulting from ATN will take several days to die from the resulting metabolic crises, and gross changes in the kidneys are expected. The general term for this predominantly degenerative type of lesion is **Nephrosis**, to distinguish it from predominantly inflammatory disease (Nephritis), but there is a degree of overlap between the two.

Character and distribution of lesions

Chemical nephrotoxicity affects both kidneys diffusely and evenly, and the dominant change is symmetrical swelling, probably largely due to leakage of filtrate into the renal interstitium. Despite the tightness of the renal capsule, this can lead to considerable renomegaly. The cut surface may appear "wet", and in some instances there is marked peri-renal oedema (something **not** seen in acute nephritis of any form). Reduced renal blood flow often produces cortical pallor to varying degrees. In some instances, mineralization of degenerate tissue will cause focal whitish spots and streaks, and perhaps a gritty texture. The intensity of all these changes can vary with particular circumstances and different toxins, and often it is not possible to grossly differentiate this lesion from some forms of nephritis (see below).

Pigment Nephrosis and Renal Microlithiasis

General

The general term "pigment nephrosis" can be applied to any state where a heavy load of pigment is accumulated in the renal tissues in sufficient quantity to cause gross renal discoloration. In one group are pigments

released into the plasma and entering the glomerular filtrate. In another group are pigments stored by metabolic disturbances such as in phalaris poisoning and lipofuscinosis.

"Renal microlithiasis" is the pathological state caused by the precipitation of crystals within the tubules. An alternative name might be "crystal precipitate nephrosis", and the archetypal lesion for this category is oxalate nephrosis. Crystal precipitation has also been seen in cases where sulphonamide drugs, administered to dehydrated animals, crystallize out in the collecting ducts, and can also be a finding in severe dehydration when endogenous solutes precipitate out at this site.

Character and distribution of lesions

In an acute severe episode of **haemoglobinuric nephrosis**, the kidneys are initially diffusely discolored brownish red to varying degrees of intensity according to severity. Any urine present in the bladder will also be discolored, and there is usually icterus and evidence of anaemia. In the ruminant world the archetypal haemoglobinuric disease is ovine (and occasionally bovine) chronic copper poisoning, with the added factor of acute hepatic necrosis and eventual bilirubinuria thrown in. This together with severe intravascular haemolysis will produce shock and hypotension, and this in turn can damage the kidneys, predisposing to some swelling as well as the discoloration.

Should the animal survive for a few days the diffuse renal discoloration disperses to become multiple streaks and foci in the cortex. With the passage of more time the residual haemoglobin is metabolized and retained as rusty-brown haemosiderin for many weeks. This is pattern is also seen in chronic relapsing haemoglobinuria.

Caprine "cloisonné kidney" is a benign pigmentary nephrosis involving the accumulation of ferritin and haemosiderin in the renal cortex, in the reticulated pattern that gives rise to the name for the condition.

Rhabdomyolyis has a similar potential to stain the kidneys, but is often not a feature of nutritional myopathies in the very young due to the low myoglobin content in the muscle of young animals.

In **bilirubin nephrosis** the kidneys are diffusely discolored to a kaki-olive drab or green/yellow shade, and if urine is present in the bladder, its froth will have a similar tone after being shaken up in a tube. Newborn calves and lambs may have congenital bilirubin nephrosis which probably reflects a temporary delay in the maturation of hepatic bile conjugation machinery.

In ovine **phalaris poisoning** greenish discoloration of the renal medulla (and cerebral gray matter) is a diagnostically useful finding although there is no renal malfunction. It is due to the lysosomal storage of indolic metabolites of the phytotoxins.

An incidental finding of this type is **melanosis**, either localized or extensive.

Acute **crystal precipitation** often produces produces pallor and a pattern of radial streaking particularly at the cortico-medullary junction. Sometimes close scrutiny of the cut surface and gentle scraping will reveal crystals to the naked eye.

Patterns of Nephritis

General

Nephritis can have infectious, toxic, or immune-mediated causes and the recognition of particular gross morphologic patterns, lesions in other organs systems and clinical correlations can provide a guide to aetio-pathogenesis. In this discussion we will refer to **five** different patterns of nephritis, categorized to give some indication of aetio-pathogenesis. As with all such schemes, it is not perfect and there are hazy and overlapping boundaries, but it basically works.

1. Interstital nephritis (also sometimes called "tubulo-interstitial")
2. Pyelonephritis
3. Septic embolic nephritis
4. Granulomatous nephritis
5. Glomerulonephritis.

At this stage it is also worth having a brief review of the **pathways of renal infection**

Infectious agents reach the kidneys via two major routes - 1) via the blood (**hematogenously**) or 2) by **ascending** from the lower tract. The agents are usually bacteria from the ano-perineal flora, and occasionally fungi.

Haematogenous infection

The characteristics of the common forms of hematogenous infection depend on the particular agent involved and exactly how it arrives in the kidneys. Thus bacteria may be "free" in the blood or carried "on board" clumps of septic embolic material of various sizes.

If the organisms are free in the blood they have the capacity to permeate the kidneys widely; if carried in emboli they will lodge wherever those emboli stick in vessels too narrow to give passage. Wherever they do end up their presence will provoke tissue injury, vigorous inflammation and therefore a form of **nephritis.** The characteristics of the inflammatory reaction will also depend on the type of agent - e.g. pus forming, granuloma forming etc.

In **leptospirosis** the organisms arrive in the kidneys via the blood, enter the nephrons and like a chemical toxin, cause diffuse **acute tubular**

necrosis, which is soon accompanied by extensive infiltration of the interstitial tissues by lymphocytes, plasma cells and varying numbers of neutrophils. There is no large scale focal destruction of tissue or abscess formation.

Small septic emboli tend to lodge in **glomeruli** and **peri-tubular cortical capillaries** although hematogenous infection can often extend right through the kidney to the deep medulla and pelvis (the renal medulla offers a very supportive environment for the growth of many organisms by virtue of its low oxygen tension, interstitial hypertonicity and high content of electrolytes and urea). The lodged emboli set up multiple small discreet sites of injury and depending on the nature of the organism, these sites may be suppurative or non-suppurative, and may predominate in the cortex **or** the medulla. This reaction is referred to as **septic embolic nephritis**.

Large septic emboli tend to lodge in **arterioles** or even **arcuate arteries** and therefore set up large focal sites of ischemic injury. This reaction is referred to as **septic infarction**, and is a serious potential complication of **bacterial endocarditis.**

Ascending infection

Particularly in female animals, the lower urinary tract is constantly at risk of bacterial infections from the heavily populated external genitalia and perineal region. Infection may ascend further to involve the **kidneys**, particularly as reverse peristalsis causes ureteral **refluxing** of septic urine during micturition.

Since the infection comes via this route the first part of the kidney to be involved is usually the renal **pelvis** and adjacent tissue, producing a **pyelitis**. Extension of the process can track it deep into the kidney and even right to the capsular surface. Because of this sequence of events the disease is called ascending **pyelo-nephritis.**

Character and distribution of nephritic lesions

Interstitial nephritis (IN) is a fairly loose term to describe a reaction pattern in which inflammation is judged to flare up diffusely throughout the kidneys, but without a focus on any particular tissue element. The formation of abscesses or granulomas is NOT a feature. Acute or subacute interstitial nephritis is the classical renal lesion of leptospirosis and malignant catarrhal fever, but is not particularly associated with any other specific **infectious** diseases. In some chemical intoxications, the initial tubular necrosis is followed by a tubulo-interstitial inflammatory reaction severe enough to be classed as IN, for instance acorn or oak-but poisoning.

In **acute leptospirosis**, renal pathology is often dominated by haemoglobinuria (see above), but if this is not present, swelling and multi-focal red/grey mottling reflect the extensive inflammatory infiltrates. In animals that survive and enter the **chronic phase**,

multiple, frequently confluent, gray/white cortical foci mark the sites of inflammation. This is not a specifically diagnostic lesion.

As interstitial nephritis of whatever cause becomes chronic, it is characterized by renal atrophy and fibrosis, rather than distortion and enlargement. In many of terminal cases it is difficult to discern what the original disease pattern may have been.

Pyelonephritis is a pattern of inflammation judged to begin in the pelvis (pyelitis) and/or peripelvic medullary tissue, from where it may extend further into the kidneys. Pyelonephritis has a couple of distinguishing features as a renal disease:

1. It always involves an **infectious agent**, usually organisms associated with the lower gut and perineal skin. Infections are often mixed.
2. It is a form of nephritis that can be **assymetric** and even **unilateral** on rare occasions.

The severity of the disease (and it can be **very** severe) depends on the destructiveness and the **extent** of the inflammation. Acute severe PN can be associated with extensive papillary/medullary **necrosis**; chronic PN with irregular **fibrosis** and either renomegaly or atrophy

Septic embolic nephritis is the pattern produced when bacteria or fungi localize at distinct multiple sites in the cortex (mostly) and medulla (less), after arriving in the bloodstream (obviously there is some overlap here with interstitial nephritis). The meat-inspection lesion known as "white spotted kidneys" in calves is an example of the process caused probably by E.Coli bacteraemia. **Septic infarction** is a more extreme manifestation of this process, and renal **abscess formation** is induced by certain agents such as *Corynebacterium ovis*, and *Arcanobacterium pyogenes.*

Granulomatous nephritis refers to the formation of distinct inflammatory masses that enlarge and distort the kidneys, usually due to sporadic infection with certain specific agents such as *Candida sp*, or other miscellaneous fungi. However, noteworthy in this context is the interesting lesion produced both in "hairy vetch" (*Viccia vilosa*) and citrus pulp poisonings in cattle.

Glomerulonephritis describes a reaction that begins with injury to glomeruli, but may extend into adjacent tubular and interstitial tissue. It is almost always caused by type 3 hypersensitivity reactions (deposition of circulating antigen-antibody complexes).

Since the pathologic processes begin in glomeruli, a major clinical feature is expected to be heavy persistent **proteinuria** ("protein-loosing nephropathy") which may progress to the **nephrotic syndrome** (hypoproteinemia and edema). Proteinuria is the result of the failure of the glomerular **protein filtration barrier**, a physiologic and structural

feature of the healthy glomerulus that in a healthy state prevents the urinary loss of plasma proteins.

As a glomerular disease intensifies, it will have adverse effects on the rest of the nephron because the renal tubules are "downstream" from glomeruli in terms of blood flow. When glomerular blood flow is impaired by glomerular disease, full-blown renal failure can ensue as tubular health and function deteriorate as well.

Macroscopically, in severe **acute** and **subacute GN**, both kidneys can become significantly **enlarged** and often mottled with a very fine pin-point stippled pattern, but they retain their basic shape.

In **chronic GN**, there is usually significant **renal atrophy and fibrosis**, with a fairly symmetrical reduction in kidney size and some distortion of shape.

Amyloidosis

General

Renal amyloidosis is a sporadic, usually idiopathic condition, and amongst ruminants most likely to be encountered in dairy cows. It is essentially an extra-cellular protein storage disease, resulting when highly protease-resistant amyloid fibrils are generated at a rate which far exceeds any capacity to remove them. Most often the disorder is of the "secondary" type, arising when precursor amyloid SAA protein is released excessively into the plasma (mostly from the liver) as one of the "acute phase reactants" in states of persistent antigenic stimulation. The stored amyloid protein is derived from SAA protein by macrophage activity and accumulates selectively at preferred sites, of which is the renal glomeruli, and interstitium are major examples .

Sometimes an associated chronic inflammatory lesion can be found somewhere in the body to provide an underlying cause, but frequently this is not so.

Clinically glomerular amyloidosis has a similar pathophysiology to glomerulonephritis, dominated by massive urinary protein loss and eventual renal failure.

Character and distribution of lesions

Even though amyloid accumulation is centered on glomeruli, the kidneys tend to become symmetrically and often massively enlarged and uniformly pale with a somewhat rubbery consistency. Close examination of the intact and cut cortical surfaces may reveal pin-point yellowish spots which correspond to glomeruli. These are clearly highlighted when the classical staining reaction is performed with acidified iodine solution. This is a quick means of grossly differentiating the disease from glomerulonephritis.

Lymphoma

General

Renal involvement in lymphoma (lymphosarcoma) is common enough and sometimes will be the most obvious gross finding. The neoplastic cells seem to prefer the cortical tissue and most of the lesions are found there. The diagnosis is fairly straightforward in those cases where distinct tumour masses are formed, but less so when neoplastic cells invade the tissue in a more diffuse manner, akin to inflammatory cells.

Distribution and character of lesions

Nodular tumour masses are white to off-white in colour, frequently bulge from the surface of the intact kidney and are not associated with any encapsulating fibrosis. On the other hand, diffuse infiltration causes irregular cortical mottling and enlargement of the kidney and can be easily confused with interstitial nephritis. In either case, an impression smear may provide a quick confirmation of the diagnosis.

Type D Clostridial Enterotoxaemia

General

Often suspected and often misdiagnosed in the midst of heat, dust, flies and rot and brought up for consideration here by the mantra "pulpy kidney". The issue of diagnostically useful renal changes is worth an airing.

Renal changes in ET across the ruminant species

The issue of accelerated renal autolysis as a diagnostic aid is really most applicable to lambs, and is of less value in adult sheep, calves, and goats. In lambs "pulpy kidneys" are not in evidence immediately after death, but can be a useful indicator in carcasses in which autolytic change is mild in other organs. In any class of animal, the evaluation of renal autolysis in a putrefying carcass is a dubious exercise. However, in lambs, sheep and calves the kidneys are frequently congested to haemorrhagic in appearance, and in calves there may be significant subcapsular haemorrhage, providing a useful piece of diagnostic evidence. Haemorrhage in the mucosa of the bladder may also be present occasionally.

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