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Clinico-Pathologic Conference: Chronic Nephritis in a Bull

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CLINICO-PATHOLOGIC CONFERENCE

From the School of Veterinary Medicine University of Pennsylvania

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Presentation of Case

*Dr. R. Marshak.**—An aged Aberdeen Angus bull was referred to the Veterinary Hospital as "an interesting case." It was not possible to obtain a past medical history or even an adequate history of the present illness. We could only learn that the animal had been "ailing for a number of weeks."

At the time of admission, the bull appeared to be thin but not cachectic, with a quiet disposition, an apparent disinclination to move about, and a dull, rough coat. There was marked ventral edema extending from the brisket to the scrotum, involving the fore- and hindlimbs. Edema of the sheath had resulted in prolapse of the preputial mucosa. However, ability to urinate was unimpaired and there appeared to be polyuria. The abdomen was large and somewhat pear-shaped. There was profuse, green, watery diarrhea. The body temperature was 101 F., pulse rate 64, and the mucous membranes were pale and slightly cyanotic. Forced exertion resulted in severe respiratory distress. The rumen was con-

*Dr. Marshak is professor of medicine.

LABORATORY DATA

URINALYSIS

	1st day	2 days later
Appearance	pale, pink-yellow clear	light pink-yellow, clear
Specific gravity	1.006	1.009
pH	7.0	7.5
Sugar	—	—
Protein	....	....
Ketones	—	—
Bile	....	....
WBC	....	....
RBC	....	occasional
Casts	....	few, fine granular
Crystals—mod. amorphous phosphates	....	....
Bacteria	moderate amount	few
Epithelia	moderate amount —renal	many—renal

HEMATOLOGIC FINDINGS

WBC	11,750
segmented	56%
nonsegmented	1%
Lymphocytes	35%
Monocytes	6%
Eosinophils	2%
Blood urea nitrogen (BUN)	102.8 mg./100 ml.
Sugar	70 mg./100 ml.
Inorganic phosphorous	8.8 mg./100 ml.

Calcium	6.7 mg./100 ml.
Total protein	3.3 Gm./100 lm
RBC	4,980,000
PCV	29%
Hb	9.6 Gm./100 ml.
Na	138 mEq./liter
K	5.4 mEq./liter
Cl	98.6 mEq./liter
CO_2	30.5 mM/liter
A/G	0.36

ASCITIC FLUID EXAMINATION

	1st day	2 days later
Specific gravity	1.009	1.009
Urea nitrogen	102.8 mg./100 ml.	104.7 mg./100 ml.
Total protein	....	136 mg./100 ml.

tracting twice per minute and the bull ate sparingly. On auscultation, the heart sounds were muffled and lung sounds were inaudible in the ventral thorax, which was dull on percussion. Abdominal paracentesis produced a clear, colorless, odorless fluid which clotted feebly.

There was slightly low amplitude in all electrocardiographic leads. The QT interval was 0.24 sec.; PR interval 0.24 sec.; and the QRS interval ~~0.21 sec~~. The electrical axis was within normal limits.

Rectal palpation was difficult to perform because of severe diarrhea and ballooning of the rectum. Rectal findings were negative.

Seven days after admission, the bull died and a necropsy was performed.

Case Discussion

*Dr. J. Buchanan.**—Based on the history and the general appearance of this animal, there seems to be chronic involvement. The most striking clinical findings are edema, ascites, and pleural effusion. Such generalized loss of fluid from the blood stream is usually caused by hypoproteinemia or cardiac failure. The most common causes of hypoproteinemia are nephritis, hepatitis, nutritional deficiency, and parasitism. These, however, need not be unrelated and often more than one is present in a given case.

There is nothing in the history or clinical findings which can be explained solely on the basis of cardiac failure. With the exception of low amplitude, the electrocardiographic findings are normal. This, together with dyspnea and cyanosis, is often found in animals with pleural or pericardial effusion or both. Pleural effusion can be caused by cardiac failure, hypoproteinemia, or pleuritis.

In the hemogram, the ratio of segmented neutrophils to lymphocytes is nearly opposite to normal. This, together with an absence of immature red blood cells and a low packed cell volume and hemoglobin concentration, leads me to consider some general intoxication of the bone marrow. However, it is also suggestive of an aleukemic leukemia. The presence of uremia is suggested by a high blood urea nitrogen (BUN), three to four times the normal value, elevation of serum inorganic phosphorus, and depresion of serum calcium. Uremia also might account for the diarrhea and for the changes in the hemogram. The albumin-globulin ratio in cattle normally is about 0.9; in this case the A/G ratio of 0.36 coupled with a total blood protein of 3.3 Gm./100 ml. indicates that there has been quite a loss of albumin. It has been stated that when blood protein drops below 5 Gm./100 ml., edema can develop in the absence of capillary damage. However, the degree of uremia present in this case indicates that some capillary damage probably has occurred. The serum sodium and chloride values are on the low side of normal. This could be secondary to the diarrhea or nephritis.

Looking at the urinalysis, we find a consistently low specific gravity. The appearance of the urine is clear though somewhat pale or pink-yellow in color. These findings would be consistent with interstitial nephritis. A 4-plus protein is strongly suggestive of nephritis and this is observed most commonly in glomerulonephritis. Bile in the urine suggests the possibility of liver damage; however, 1-plus is not very significant. The absence of casts in the first urine sample might be misleading. In interstitial nephritis, granular casts are frequently present unless the urine is alkaline as in this case. Moderate amorphous phosphate crystals are normally present in alkaline urine. The presence of moderate to many renal epithelial cells suggests tubular damage.

The specific gravity of the ascitic fluid is about the same as that of the urine. There is a high level of urea nitrogen present and there was a small amount of protein in the sample taken two days after admittance. The low protein and specific gravity of the ascitic fluid suggests that it is a noninflammatory transudate rather than an inflammatory exudate.

I would now like to discuss my original statements concerning the causes of edema. The possibility of poor nutrition cannot be evaluated because of the inadequate history. The degree of parasitism also cannot be evaluated, since a fecal examination was not reported in the laboratory data. I think that fecal examination should be done in any case of anemia or edema

*Dr. Buchanan is instructor in cardiology.

or both. However, the age of this animal makes it unlikely that poor nutrition or parasitism is responsible for the edema. I would consider that edema related to cardiac problems is a secondary factor in this case since the laboratory findings related to uremia would account for the clinical condition of this animal. My inclination at this time is to consider nephritis as the primary problem.

Pyelonephritis caused by *Corynebacterium renale* is a common disease in cattle; however, it is not common in bulls. In this disease, the urine is stringy, viscid, and dirty gray or often bloody, whereas in this animal the urine was clear. This makes me less suspicious of pyelonephritis. Traumatic pericarditis is a possibility. However, such animals often have signs of traumatic gastritis. I don't believe there are indications that this was the case in this animal, as the rumen was active, with a rate of about two contractions per minute. Brisket disease might be considered. Again, the history does not indicate that this animal was being subjected to altitude changes, and I think that the evidence of nephritis would make one less suspicious of brisket disease. Other things to consider as causes of nephritis might be poisoning, secondary involvement to some pyogenic infection elsewhere in the body, or therapy with drugs such as sulfonamides or certain anthelmintics.

The primary diagnosis in this case is chronic interstitial nephritis with some degree of glomerular involvement to account for the loss of protein in the urine.

Dr. R. S. Brodey.—Why did you use the term "interstitial nephritis"? My understanding is that it is primarily seen in dogs and is rather unusual in cattle where pyelonephritis is the common finding.

Dr. Buchanan.—I use the term "interstitial nephritis" because the urine has low specific gravity and is clear. Pyelonephritis, on the other hand, is rare in the bull and can be diagnosed quite easily by urinalysis. The urine is gray, appears "dirty," and there are blood clots, epithelial matter, and bacterial cells which have a tendency to clump and form a distinct layer when the sample is centrifuged. Also, pyelonephritis seldom reaches the stage of uremia. In glomerulonephritis, the specific gravity is generally elevated and there is oliguria rather than polyuria. I hesitate to pinpoint a pathologic diagnosis. I prefer to say that the case is one of nephritis.

*Dr. D. Cohen.**—Why did you not mention leptospirosis in your discussion?

Dr. Buchanan.—Uremia in cattle is not a clinical characteristic of leptospirosis in this country where the most common serotype is *Leptospira pomona*. It is reported to occur frequently in Israel in cattle infected with *Leptospira grippotyphosa*.

*Dr. W. D. Malherbe.***—I've had the opportunity of discussing this case with Dr. Buchanan and I think that we are in agreement on it, particularly the very definite involvement of the kidneys. While I was sitting here, though, I was thinking that if I were back home in South Africa I would be almost certain to make a diagnosis of liver fluke infection. I don't know if you see it here, but this is a classical picture of *Fasciola hepatica* infection. The edema, the low albumin, and the diarrhea are characteristic. Dr. Buchanan did mention the lack of a fecal examination here which I think would be rather important in such a case. In addition, I might say that some liver studies should have been made; the only evidence we have on the status of the liver is 1-plus bile in the urine. I'd have liked to have had more definitive tests of liver function because, generally speaking, I'm not much impressed with the kidneys as a big loser of albumin in animals. With such a low serum albumin, I definitely want more information about the liver. Please understand that I am not discounting the kidneys—they are definitely involved—but some of these other things, particularly the edema and the low serum albumin value, require explanation.

Dr. R. S. Brodey.—Would you expect an animal with a liver fluke infection to have such an elevated BUN?

*Dr. Cohen is assistant professor of veterinary public health.

**Dr. Malherbe is visiting professor of clinical laboratory medicine.

Dr. W. D. Malherbe.—Kidney involvement, I think, is not in question at all; it is definitely present—we are dealing with an old bull. What I've really been trying to do is to explain the low albumin and the presence of the widespread edema which I don't feel are explained by the kidneys alone.

Dr. R. R. Marshak.—Even with a chronic 4-plus proteinuria?

Dr. W. D. Malherbe.—Well, in the absence of actual figures on what that albumin amounts to, one is usually surprised to find how little albumin is lost over 24 hours if you do actual determinations. However, we don't have figures here, so we'd only be guessing. In the nephrotic syndrome in man this plays a big role, but in animals it seems to be subordinate to liver as an albumin loser.

Dr. J. E. Prier.—To me, the outstanding deficiency in this case is the failure to culture for bacteria. I presume there is a reason for this, but I also presume that the necropsy does not have the same deficiency.

Clinical Diagnosis

Chronic nephritis with glomerular involvement.

Pathologic Findings

*Dr. R. M. Sauer.**—On primary incision, edema found in the subcutaneous tissues was 3 or 4 cm. in depth and moist (this was noticed clinically). The subcutaneous fat contained many flecks of white, opaque chalky material which on histologic examination proved to be necrosed fat. Fat deposits everywhere in the body had a similar appearance, especially in the pericardium and the mediastinum where large masses of a firm, white, and soaplike fatty material were found. Also, several gallons of clear, watery fluid were present in the abdominal cavity. The thoracic cavity was approximately half-filled with a clear serous fluid which clotted upon standing. Upon examination of the pancreas, there were large disseminated areas which appeared firm, white, and soapy, and these infiltrated the spaces between what appeared grossly as normal lobules. The kidneys were of normal size, grayish, and firm. The capsule stripped with ease. The surface was uniformly granular, or what some might call finely pitted. Resistance to cutting was greater than normal. The cortex was mottled with gray and the cortical striations were indistinguishable. The glomeruli appeared as minute waxy bulging hemispheres and stained with Lugol's solution. The liver was not remarkable either grossly or histologically. Histologically, there was chronic pancreatitis and, as I mentioned before, the adipose tissue everywhere contained soaps. The kidney was in an advanced state of amyloidosis. Chronic nephritis was also present.

These were the pertinent findings and the final diagnosis was chronic nephritis with amyloidosis or the reverse, whichever you might consider to be the more important. A diagnosis of fat necrosis should also be mentioned and may be pertinent as regards the cause of the amyloidosis. In my opinion, the chronic nephritis is probably secondary to the amyloidosis.

There are many interesting things in this case which I think need explanation. The first is fat necrosis. In cattle, fat necrosis involving the abdominal cavity can possibly be explained (as in dogs) on the basis of a pancreatitis which we did have in this case. In many other cases we haven't been able to point this out. It is hypothesized that pancreatic enzymes released into the lymphatics pass all the way around the abdominal cavity and may even pass into the thoracic cavity. This is a possible explanation for the soaps that we find in the pericardial sac. One thing that is difficult to explain is the presence of fat necrosis in the subcutaneous tissues. In many instances this is explained as a result of trauma or something of this nature, but to me, in this particular case, it would seem that it is part of the systemic involvement. The distribution of the amy-

*Dr. Sauer is assistant professor of veterinary pathology.

loid was extremely interesting. Histologically it involved the glomeruli; the capillary tufts of the glomeruli were almost completely obliterated. Amyloid was also found around the tubules especially in the cortex and around blood vessels. Supposedly, uremia develops from amyloidosis due to interference with the blood supply. The encroachment upon the blood vessels causes anoxia and this in turn can produce degeneration of the tubules; nephritis can be secondary to this.

Dr. R. R. Marshak.—One of the cardinal signs of amyloidosis in cattle and other species is excessive proteinuria. In cattle, where this is not a common finding, as Dr. Malherbe pointed out, I always think of amyloidosis whenever I see a chronic severe proteinuria. I would guess that the amyloidosis was secondary to the nephritis rather than the other way around—this is the usual explanation that is offered in discussions of amyloidosis in the literature. Also, I was struck by the resemblance of this whole syndrome to the nephrotic syndrome in man. Everything was there except we didn't measure the degree of lipemia—there was albuminuria, hypoalbuminemia, edema, and ascites. Another thing about fat necrosis in cattle is that the quality of dietary fat may be involved.[1] Unfortunately, I could not obtain this animal's dietary history, but cattle eating long-chain saturated fatty acids or their esters are supposed to develop fat necrosis. The other possibility, I suppose, is that pancreatic enzymes might be circulating in the blood and in this way reach fat all over the body.

Dr. W. D. Malherbe.—I would like to raise the question as to whether a lack of pancreatic enzyme could be related to the hypoproteinemia?

Dr. R. R. Marshak.—I presume it could have been a contributing factor, but I think that this bull must have had a 4-plus proteinuria for weeks and maybe months, and I think that this excesive proteinuria alone could easily account for the hypoproteinemia.

Dr. R. M. Sauer.—There is one other point that I'd like to mention. I was interested to hear you say that the amyloid is considered secondary to the nephritis. In the classification of amyloidosis, one considers primary and secondary amyloidosis. The secondary is the most common form occurring in animals and is usually said to be associated with a protracted primary disease with extensive tissue breakdown. I don't believe that primary amyloidosis has ever been seen in animals. There is also a difference in distribution so that, in the primary form, amyloid is usually found in muscles and heart; while, in the secondary form, it is in the kidney, spleen, and liver.

Dr. R. R. Marshak.—A type of systemic amyloidosis has been reported in horses frequently given injections of antigens for production of hyperimmune serum.

Dr. R. M. Sauer.—Coming back to secondary amyloidosis, this is usually considered to be related to some necrotic process which is going on in the body—in this case, it may have been related to fat necrosis. What are your thoughts about the relationship of the nephritis to the amyloidosis?

Dr. R. R. Marshak.—In man, chronic nephritis can be the inciting cause.[2] It is one of the conditions associated with tissue destruction and infection which can result in the deposition of amyloid.

Dr. J. E. Prier.—I get the very distinct impression from this discussion that you have been talking about secondary effects being caused by secondary effects, and I wonder if you would care to make a statement as to what you think a primary cause might be? And again, I would ask the question as to why, with nephritis and pancreatitis, there were no cultures taken at necropsy?

Dr. R. M. Sauer.—To summarize, it looks as though two possibilities exist. In one, chronic pancreatitis produces fat necrosis which leads to secondary amyloidosis and in turn to nephritis. In the other, chronic nephritis leads to amyloidosis, the pancreatitis and fat necrosis being unrelated.

*Dr. W. Lawrence.**—I am puzzled as to why pancreatitis is always invoked to explain fat necrosis, since I consider it unlikely that an individual's enzymes are capable of digesting his own tissue. Also, in view of the fact that enzymes are quite specific with respect to pH requirements, temperature, substrate, and so forth, I do not think that leakage of pancreatic enzymes would explain such lipolytic activity.

Dr. R. R. Marshak.—This view is based upon certain types of experimental evidence. For example, pancreatic enzymes injected into the abdominal cavity have resulted in digestion of fat leading to fat necrosis. The fat is hydrolyzed to glycerol and fatty acids. The fatty acids combine with metallic ions to form soaps. I think that it is entirely possible for an animal's lipolytic enzymes to digest its own fat when in contact with such fat. The enzymes of the pancreas—not insulin and glucagon, of course, but the digestive enzymes of the pancreas—are intended only for secretion into the gut and not anywhere else. It is also interesting that you can often correlate the finding of fat necrosis with a degree of pancreatitis.

Dr. R. M. Sauer.—I think this is sometimes harder to explain in the cow than it is in the dog the cat. In the dog and the cat, pancreatitis and fat necrosis occur rather frequently and the necrosis is usually limited to the fat right in the area of the pancreas. I think the huge masses involving all of the fat in the abdominal cavity of cattle is sometimes harder to explain on this basis.

Dr. J. E. Prier.—Getting back to my original complaint; as I understand it in this bull, the disease is blamed primarily on his chronic interstitial nephritis. Now my question, then, is this: What is suggested as the cause of chronic interstitial nephritis in cattle?

Dr. R. M. Sauer.—This is a logical and pertinent question but the etiology cannot be fully explained because of the lack of bacteriologic evidence. There are primarily two types of interstitial nephritis, one of which, in man at least, is associated with toxins following streptococcic and leptospiral infection. This is a diffuse interstitial type of nephritis. The other type is a focal form in which the bacteria themselves lodge in the kidney and spread through the interstitium. This is spoken of as "pyelonephritis" and may be ascending or hematogenic. Now, as far as animals are concerned, cultures have not often been attempted and, in many instances, there is superficial evidence to the effect that existing infection elsewhere in the body might possibly produce whatever these substances are that are necessary to damage the kidney. However, this hasn't been worked out in animals. It is something which should be studied so that the whole problem of nephritis in cattle or in dogs (where it's probably most common) can be better understood.

Dr. R. R. Marshak.—One thing that I would add, Dr. Prier, is that at this stage of the game whatever you got out of culturing the kidney or the urine would almost have been academic (although I think it would have been nice to have done it). One would be hard put to feel that he could then readily relate this to the renal lesion at this particular stage of the disease process. Whatever the inciting cause was, it must have taken place long ago in this case. The pathogenesis of the amyloid process of the kidney in cattle is probably similar to the pathogenesis of amyloid kidney in man. This lesion in the cow is apparently quite rare.

Pathologic Diagnoses

1) Amyloidosis of the kidney.
2) Chronic nephritis.
3) Chronic pancreatitis.
4) Generalized fat necrosis.

References

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*Dr. Lawrence is instructor in virology.