1976

Bovine Lymphosarcoma

Ronald Hinze
Iowa State University

Bruce Hull
Iowa State University

Follow this and additional works at: https://lib.dr.iastate.edu/iowastate_veterinarian

Part of the Large or Food Animal and Equine Medicine Commons, and the Oncology Commons

Recommended Citation
Available at: https://lib.dr.iastate.edu/iowastate_veterinarian/vol38/iss2/6

This Article is brought to you for free and open access by the Journals at Iowa State University Digital Repository. It has been accepted for inclusion in Iowa State University Veterinarian by an authorized editor of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.
Bovine Lymphosarcoma

by
Ronald Hinze*
and
Dr. Bruce Hull, DVM, MS†

SUMMARY

Lymphosarcoma is a major problem among some herds of dairy cattle across the United States. A C-type RNA virus has been isolated and is thought to be the incriminated agent that causes the adult form of lymphosarcoma.

Lymphosarcoma manifests itself in many ways, usually mimicking many other disease entities, thus confusing the diagnosis of other diseases. One consistent specific finding is the enlargement of the visceral and peripheral lymph nodes throughout the body.

This paper will discuss the many aspects of the problems and concepts of adult bovine lymphosarcoma.

CLINICAL CASE REPORT

A Holstein dairy cow was presented to Stange Memorial Clinic on December 16, 1974. Examination of the cow revealed:
1. Swelling anterior to the right rear leg that started (or was noticed) several weeks prior to the time of entry.
2. Normal temperature.
3. Enlarged left prefemoral lymph node.
4. Prescapular lymph nodes were enlarged.
5. Respiratory rate and depth appeared normal.
6. Some hemolymph nodes appeared enlarged.
7. All palpable visceral lymph nodes were enlarged.
8. A rectal exam revealed that the cow’s iliac lymph nodes were approximately five to six times their normal size, and

†Dr. Hull is an Associate Professor in Veterinary Clinical Sciences at Iowa State University.

* R. Hinze is a fourth year student in the College of Veterinary Medicine, Iowa State University.

NADC agreed to buy the cow from the owner. NADC’s primary interest in the cow was her pregnancy. They wanted to test the possibility of vertical transmission of the leukemia virus from mother to offspring.

On post mortem, the seven month old fetus was taken and cell cultures were

that the cow was approximately seven months pregnant.
A blood sample was drawn and sent to the laboratory for examination. The results were:

| Hemoglobin | 10.7 |
| PCV        | 32.1 |
| WBC        | 18,400 |

Differential

49% segmented
49% lymphocytes
2% eosinophils

platelets adequate
plasma protein 8.5
fibrinogen 500

A serum sample was sent to NADC for a serology test for the leukemia type C virus. The results were strongly positive for the C-type RNA virus.

A biopsy was taken of the prefemoral lymph node and sent to pathology for examination. The report revealed the normal lymph node architecture was obliterated by neoplastic lymphocytes. The capsule was thickened with excessive granulation tissue and infiltrated by pleomorphic lymphocytes. Mitotic figures were quite numerous. All these findings led to the conclusion that the animal had lymphosarcoma.

NADC agreed to buy the cow from the owner. NADC’s primary interest in the cow was her pregnancy. They wanted to test the possibility of vertical transmission of the leukemia virus from mother to offspring.

On post mortem, the seven month old fetus was taken and cell cultures were
innoculated, but no virus was isolated from them. A lymphocyte suspension was also done, but no virus was isolated there either. They also collected 250 ml. of blood from the cow and recovered the buffy coat which contains the lymphocytes. A calf from a known non-infected cow, taken immediately after birth, was fed one quart of milk and two hours later it was fed the leucocytes from the 250 ml. of blood. The calf at seven months of age is serologically positive for the C-type RNA virus, but no virus has been isolated from the calf as yet, and no clinical signs have been seen. If the cow had been a very avid virus carrier, an infection of the calf with virus being isolated, should have been seen about two or three months after infection.

**DISCUSSION**

Bovine lymphosarcoma is a malignant invasive tumor of lymphocytes or lymphoblasts. It is the most important, but not the most frequent, neoplasm of the bovine species. 5

Lymphosarcoma, not to be confused with lymphoma, which is a benign tumor of lymph nodes or other lymphatic tissue, manifests itself in four major forms. The first usually occurs from birth to six months of age. It presents itself in a calf that is gradually losing weight and then gets a severe lymphadenopathy. Usually there is also proliferation of lymphoreticular tissue in the lymph nodes, spleen, and bone marrow. The second form usually occurs between six and thirty months of age. This is the thymic form, which is usually the infiltration of the thymus by neoplastic lymphocytes. The third type occurs from about eighteen to twenty months of age and is the cutaneous form. This is usually called sporadic bovine leucosis where cutaneous plaques 1-5 cm. in diameter appear on the neck, rump, or thighs. An intradermal thickening is usually seen, but there is no discontinuity of the epithelium. The hair is covered by a thick gray-white scab or else it is shed. These may look like an urticaria type change in the skin. After healing they will have an increased skin sensitivity in that specific area of the body. Recurrences are quite common for one to two years. The fourth type, which constitutes the majority of this paper, is the adult form of lymphosarcoma. Usually the adult bovine between the age of four and eight years will be affected. An irregular lymphadenopathy and frequent infiltration of heart, abomasum, and intestine may occur. Bone marrow, liver, and thymus are rarely involved, but usually spleen, lungs, kidneys, adrenals, pancreas, skeletal muscle, and udder are secondarily involved by this rapidly spreading neoplastic disease.

Bovine lymphosarcoma has been diagnosed in approximately 17.5 cases/100,000 head 5 in the United States. There does not appear to be a breed or sex predisposition that is more affected by lymphosarcoma. Any age animal is susceptible, but it appears to be most prevalent in animals that are from four to eight years of age.

A California purebred herd of dairy cows had five clinical cases in five years. 3

Hemograms of all the mature cows at this farm were taken and it was found that a large number had a leukocyte pattern that indicated a blood disorder in the lymphocytic series. Usually in a herd such as this, two to five percent of the animals will develop lesions per year, which leads to weight loss and flesh loss that ends quite soon with death.

Dairy cattle appear to have more lymphosarcoma than beef. In a test run where 4,394 cattle were tested, 450 (10.2%) were positive in the dairy cattle category. 2794 beef cattle were tested and 35 (1.2%) were positive. This is a much smaller number than the dairy cattle affected. Dairy cattle are kept in close confinement and usually have an older average age, so it can be expected that more will be of the dairy cattle type.

There are two major adult types which are normally found in the bovine. The first is a subclinical case where the reticuloendothelial system is stimulated and a lymphocytosis is present. This may persist for the life of the animal without the appearance of neoplasms. The second is a clinical phase which progresses from the subclinical to the clinical form when neoplasms are present. This may be acute or chronic, but it appears to always be fatal.

Iowa State University Veterinarian
because of its invasive and metastatic properties.

A C-type RNA virus approximately 100-200 millimicrons in diameter has been incriminated as the cause of bovine lymphosarcoma. A method of culture of this virus was not reported until 1969. The specific virus will cause leukemia in cattle and sheep, and can be transmitted from cattle to sheep, also. After the virus is present in the body, the body will develop antibodies against the virus. These antibodies can then be diagnosed by precipitation in the gel diffusion test, or by use of immunofluorescence. By the use of immunofluorescence it is known that cat, mouse, and human leukemia virus are not related to the bovine leukemia virus. The presence of antibodies in the blood stream of bovine does not necessarily mean that the animal has the virus presently, but it simply means that it previously carried the virus or has it now.

A transmissible viral agent has been isolated in the milk of a herd that has lymphosarcoma. This virus-like particle resembles the RNA-C type virus but it hasn’t been positively identified. Researchers have come to the conclusion that the virus can be shed in the milk by studies which they have been doing. This same virus particle has been seen in the blood serum from animals that are known to be infected with lymphosarcoma.

Lymphosarcoma has been transmitted with cellular material, cell free and bacteria free material from leukotic cattle. The cattle which these extracts have been injected into have developed lymphosarcoma. If viral particles are experimentally transmitted to calves, the viral particles and antibodies can be demonstrated within three to four months after injection. Outward signs are not necessarily seen, but a lymphocytosis may be seen.

Diagnosis can usually be made by gross physical exam of the animal at the time the farmer calls you to his farm. Smith reported that 85% of lymphosarcoma suspects could be diagnosed grossly without laboratory help. This doesn’t include the very early type where no lymph nodes or organs are involved.

Lymph node biopsy is probably the best and most reliable method of confirming a diagnosis because direct examination of the lymphocytes in the lymph node can be made.

Blood may be drawn and the total and differential white blood count can be looked at. One cannot be 100% positive that an animal has lymphosarcoma, but he can get a better feel for a positive diagnosis. Blood serum can be drawn and sent to NADC where several tests can be run. These are gel diffusion, indirect immunofluorescence, and complement fixation. The clinical pathology aspect will be discussed later.

The clinical signs of lymphosarcoma can be manifested in a multitude of different ways. The most obvious lesion seen by veterinarians on the farm is the enlargement of the peripheral lymph nodes. Approximately 75-90% of the animals will show this. The major lymph nodes that are usually seen are the prescapular, mandibular, and the prefemoral. The retropharyngeal lymph nodes and the internal thoracic lymph nodes may also become enlarged and cause severe dyspnea to the animal. A persistent snoring sound may be the first evidence that a farmer notices. This must be differentiated from actinobacillus and tuberculosis, which could cause similar sounds. If the thoracic lymph nodes are enlarged, there is a good chance that it will spread to the heart. If this happens, congestive right heart failure appears to be a prominent sign. Hydropericardium with muffled heart sounds is usually present; enlargement of the jugulars, edema of the brisket, and sometimes hydrothorax are also seen. Often times the lymph nodes will put pressure on the esophagus and cause severe bloat because of the stopping of eructation of gases from the rumen. Traumatic pericarditis and severe endocarditis must be considered in the differential diagnosis here.

Blood stasis in the digestive tract due to the congestive heart failure may predispose the animal to diarrhea and an enlarged liver with secondary liver problems. A severe diarrhea should be differentiated from a severe bacterial diarrhea such as salmonella, Johnes disease, or mucosal disease. Each must be considered individually as a possible diagnosis. If blood
specks are seen in the feces, it could be severe bleeding in the abomasum from an ulcer that is located within the wall. Parasites must be considered here, especially coccidiosis, in your diagnosis. A rectal exam may be helpful in your differential, as it will usually reveal enlarged abdominal lymph nodes, especially the internal iliacs.

A rapidly growing neoplasm may elicit a temperature response in a cow of 104-105°F. The temperature is due to the increased neutrophil numbers which are increased to take away the necrotic centers of the lymph nodes. Usually the blood supply is outgrown and cannot support the neoplastic mass which will lead to central necrosis of the lymph node.

The uterus may feel very nodular and hard, but may still maintain a pregnancy, as was the cow in the clinical case. This must be differentiated from fat necrosis in the uterus, a mummified fetus, or an adenocarcinoma which usually runs in rings across the uterus. It has also been incriminated as a cause of infertility, dystocia, and abortions in adult cows. The nervous form appears much the same as lead poisoning, an abscess in the brain, rabies, or an injured portion of the vertebral column. Usually this form has a gradual onset over several weeks. Sensation is kept, but the motor aspects appear to be lost so the animal is unable to get onto its feet. It has a progressive worsening until death of the animal. Sometimes it will metastasize to the brain or cranial meninges and act as a space occupying lesion that has localizing signs. A cerebral spinal tap is of much benefit in helping to diagnose between these different possibilities. A proportion (5-10%) run a peracute course and the affected animals often die without showing prior signs of illness. Involvement of the adrenal gland, rupture of an abomasal ulcer, and rupture of an affected spleen followed by acute internal hemorrhage are known causes of such terminations. Such animals are often in good body condition.

A tabulation of affected organs was kept to show which had the greatest incidence. It appeared as thus: 7

<table>
<thead>
<tr>
<th>Organ</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>abomasum</td>
<td>90%</td>
</tr>
<tr>
<td>heart</td>
<td>76%</td>
</tr>
<tr>
<td>kidney</td>
<td>53%</td>
</tr>
<tr>
<td>spleen</td>
<td>48%</td>
</tr>
<tr>
<td>uterus &amp; vagina</td>
<td>45%</td>
</tr>
<tr>
<td>liver</td>
<td>38%</td>
</tr>
<tr>
<td>intestine</td>
<td>31%</td>
</tr>
<tr>
<td>orbit</td>
<td>31%</td>
</tr>
<tr>
<td>lung</td>
<td>21%</td>
</tr>
<tr>
<td>mammary gland</td>
<td>8%</td>
</tr>
<tr>
<td>adrenal</td>
<td>5%</td>
</tr>
</tbody>
</table>

Many times the initial lesion will metastasize to an area where there is no lymphoid tissue, such as skeletal muscle, kidney, liver, or into the retrobulbar area causing panophthalmitis. After a complete post is done, the animal has very few organs that are not affected by the neoplastic lymphocytes throughout the body.

Lymphosarcoma appears to be propagated in certain blood lines as a hereditary trait. If a bull, who is carrying the leukemia virus, breeds a cow, the resulting calf has a high possibility of carrying the virus also. It appears as though it is passed through the semen from the bull to the calf.

In Weischer, Germany, 149 of 150 progeny of one specific bull came down with clinical signs between the ages of one to six years. Usually the adult form’s signs don’t show up for four to six years because of the long incubation period of the virus, which is about four years.

Lymphosarcoma could be spread by placenta, milk, or colostrum. If a cow that is a known carrier of the leukemia virus has a calf, it is best not to introduce milk or colostrum to this calf from its own dam, but rather colostrum from another cow that is known to be negative. It appears usually the leukemia virus may be introduced during the fetal period of life, but our clinical case doesn’t support this. As stated before, the virus particles have been isolated from the milk and colostrum.

Most dairy farmers acquire the disease by introducing a subclinical case of either a cow or a calf onto their premises. Bulls can actively spread the disease if they are carriers, but AI semen has not been linked directly with carrying the virus. More tests are still being done on AI semen. Suspicions have been made that hypodermic needles and blood transfusions
are also possibilities for spreading of the disease—circumstances that could condemn the veterinarian. As can be seen here, both vertical and horizontal transmission appear to play a role in the different types of transmission.

Clinical pathology can be an advantage to the veterinarian to help diagnose lymphosarcoma. Many cows have a lymphocytosis prior to the time that tumorous masses will develop. A total white blood cell count could be anywhere from 6,000 to 600,000. At the high level a high percentage of the WBC’s may be lymphocytes, but usually this occurs in only a minority of the cases. Oftentimes you will see a moderate neutrophilia along with the lymphocytosis, which is due to necrosis of cells within the tumorous mass because of its limited blood supply.

In subclinical cases of lymphosarcoma changes can be seen in the lymphocytes in the bloodstream. Specific signs which can be looked for are: 1) increased number of lymphocytes and lymphocyte-like cells in the blood. 2) pathological cells of the mononuclear type. These are usually large lymphocytes 15-25 microns in diameter, and are irregularly shaped with the nucleus deeply colored and usually a small amount of cytoplasm is present. The nucleus is large, eccentric, and oftentimes bizarre shaped.

Bone marrow necrosis may also be seen. This will be associated with the anemia.

A pattern which is often followed when looking at a blood smear would be if greater than 25% of the lymphocytes are atypical the blood sample is considered a suspect. If greater than 50% are atypical, a diagnosis of lymphosarcoma can be made with confidence.

Other ways of diagnosing lymphosarcoma are 1) resecting a lymph node or lymph node biopsy 2) culturing for the leukemia virus, but this method is quite expensive 3) antibody demonstration of suspected virus.

No agent has been found that will completely cure the animal of lymphosarcoma. Nitrogen mustards at 30-40 mg daily for 3-4 days has caused temporary remission of signs. Triethylenemelamine has also been used and shown some improvement, but no anti-cancer drugs are feasibly significant to use in the bovine species.

Post mortem findings will often help support your preliminary diagnosis of lymphosarcoma. Lymph nodes will usually be enlarged (three times or greater) throughout the body, especially the abdominal, prescapular, and mandibular lymph nodes. The color of the nodes vary quite extensively from grayish white to a yellowish pink. Usually they are quite resilient, smooth surfaced, compact in consistency, and painless.

In lymphosarcoma the abomasum has thickened wall in many cases, which occasionally is ulcerated due to the occlusion of the blood vessels in the submucosa by tumor cells. If ulcerations are seen, this will usually lead to a tarry black stool.

Uterine tumors are quite rare, but if present there usually is a plaque like thickening in the wall. The tumor will be a gray-white color and quite compact. The cow may be pregnant while the wall is being infiltrated with neoplastic lymphocytes. The uterus may also appear to be enlarged.

The right atrial wall is usually the primary site in the heart that neoplastic lymphocytes will invade. A thickening, or nodule, is usually formed in the wall and is quite obvious when the heart is opened up upon necropsy. Oftentimes a hydrothorax or hydropericardium and brisket edema are seen due to right heart failure.

Neoplastic lymphocytes may enter the spinal canal and put pressure on the cord leading to posterior paralysis with a gradual onset over a several week period. The most common site for the lesion is at the last lumbar or first sacral vertebrae. Metastasis to the cranial meninges is quite likely, or it could be the primary site for a lesion.

Neoplasms such as these can be recognized microscopically by change in size, structure, or form of a specific organ. For microscopic diagnosis areas that are suspected to be tumorous should be removed and cut into cubes ½” wide. They should be fixed in 4% formaldehyde and sent to the laboratory for examination. Heart, particularly the right atrium, liver, spleen, and lymph nodes are the major organs that should be sent.

Microscopically the organ will contain
highly neoplastic lymphocytic cells that usually obliterate the normal architecture of the organ. Usually in their growing process, which is quite rapid, they will outgrow the limits of the capsule around the organ. The neoplastic cells are very pleomorphic and often will manifest themselves as being irregularly spherical with a narrow zone of cytoplasm around the eccentrically located nucleus. The nucleus is spherical and strongly basophilic staining, oftentimes showing mitotic figures.

The possible spread of the disease from cattle to man has been proposed, but an epidemiological survey has shown that there was no significant difference of incidence between farms that had lymphosarcoma virus and farms that did not have the virus, with respect to the death rate from lymphosarcoma in humans. Laboratory personnel, dairymen, and eighty veterinarians were tested in another study and no correlation could be found. In another study, fifty human subjects with various forms of leukemia were tested and identification of the virus was attempted, but no correlation between human leukemia and the bovine leukemia virus was seen.

Specific lymphosarcoma virus particles will stimulate antibody production in the serum. If these virus particles are added to unpasteurized milk, which is then pasteurized, no infective agents are transmitted to animals that are tested with this milk. Therefore, man should not worry about drinking milk from cows that are carrying the leukemia virus.

If an animal is hematologically diagnosed as being positive for lymphosarcoma but no gross lesions are seen on the animal at the time of slaughter, there is no reason why the animal’s meat should not be consumed by man.

Specific control measures for herds with lymphosarcoma are quite hard to assess since the properties of the C-type RNA virus are not well known. Europe, especially Denmark, has set up specific slaughter and eradication programs which seem quite drastic, but the incidence of the disease is quite high in areas of that country. Other European countries have segregated the affected or positively diagnosed cattle from the negative. As I pointed out previously, some families of cattle are predisposed, so people of Europe are trying to prevent entrance of these cattle into their herds. Today Denmark has a specific control program that consists of: 1) sale of animals that are infected other than for slaughter is prohibited; 2) contact of infected animals with those in free herds is prohibited; 3) spread of contagious material is prohibited. This has helped tremendously by decreasing the number affected by one-third over the last ten years.

Calves born to a lymphosarcoma positive dam should not have the colostrum from that dam because the virus is known to spread through the colostrum. If this calf would be from Denmark, it would be tested three times if the intention was for it to be a replacement heifer. The time interval would be six months, one year, and two years. If all these were negative, the animal would be considered negative.

The U. S. herds that have positive cattle have not gone to the radical treatment of total slaughter probably for the simple reason that it isn’t economically feasible. Thought has seriously been given to prevent movement of diseased cattle into herds that do not have a problem as yet.

Recommendations about the clinic case herd consisted of several things. The first and most logical was disbanding of the complete herd, but this would lose all the breeding stock that he had acquired over the past years. The second would be to keep the calves from getting colostrum from positive cows. They would have to be kept completely separate from the other animals. In time the positive cows would be eliminated from the herd and a negative herd would dominate. This would be very difficult since two complete herds would have to be kept on the same farm, especially using the same parlor.

Lymphosarcoma is a problem of bovines across the world. As more research is done on the problem, we will learn how to cope with the problems. Hopefully in the future anti-cancer drugs will be of some benefit so the high genetic quality stock may be saved and the disease incidence decreased.
REFERENCES

14. VanDerMaaten, Dr., Telephone interview.