A Review of Bovine Leukosis

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Bovine leukosis was first recognized in Europe in the latter part of the 19th century. During the early 1900's, clinical reports of the disease continued to appear in the veterinary literature, not only in Europe but also in the United States. Veterinarians in Germany observed that many epidemiologic features of leukosis suggested it might be infectious, i.e., cases were clustered in certain herds and in limited geographic regions, and the disease was spreading from these herds or areas into previously leukosis-free cattle populations. Hematologic studies were conducted in affected herds and researchers found that many of the clinically healthy cattle had a continuously elevated number of peripheral blood lymphocytes. They termed the condition persistent lymphocytosis and proceeded to use this rather non-specific parameter as a diagnostic test for subclinical bovine leukosis. Some countries even established control programs for the disease which were based on use of the hematologic keys to identify affected cattle. One of the best-known keys was developed by Bendixen in Denmark and consequently the blood examination was frequently referred to as the Bendixen test.

It was also Bendixen who conducted epidemiologic studies that resulted in the recognition that there were different clinical forms of leukosis in cattle. He described juvenile and cutaneous forms, which were relatively rare and occurred randomly in the Danish cattle population. These 2 forms were therefore classified as sporadic bovine leukosis. The more common form, which was associated with persistent lymphocytosis and appeared to be infectious, was termed enzootic bovine leukosis. Other workers subsequently confirmed the validity of Bendixen's observations and further subdivided juvenile leukosis into calf and adolescent thymic types. An excellent clinical and pathological description of all 4 forms of bovine leukosis was presented by Stober to the American Association of Bovine Practitioners in 1981 and the reader is referred to the proceedings of that meeting for details. Briefly, however, the forms are characterized as follows: calf—usually occurs in animals less than 6 months old and presents as a generalized lymphoid neoplasia involving all hematopoietic tissues and most of the major body organs; thymic—effects animals 6 to 30 months of age, tumor is restricted to the thymus and local lymph nodes; cutaneous—seen in cattle 1 to 3 years old, skin tumors usually disappear (this is the only non-fatal form of bovine leukosis); adult or enzootic—occurs in older animals, usually over 4 years, with tumors randomly distributed in 1 or more lymph nodes and also in other tissues, especially the heart, abomasum, spleen, kidney, and uterus.

In 1969 a virus was isolated from typical cases of adult type bovine leukosis and subsequent research confirmed that it is the primary etiologic agent of the infectious tumor which Bendixen called enzootic bovine leukosis. The remainder of this paper will deal solely with the bovine leukemia virus (BLV), its characteristics, transmission, diagnosis, oncogenicity, and significance to the cattle industry of the United States.

What type of virus is BLV?

Taxonomically, BLV is classified as a retrovirus. The most significant attribute of agents in this category is the ability to establish persistent infections in the host. The mechanism for persistence is mediated by a specific viral enzyme known as reverse transcriptase. Using this enzyme, the virus can make DNA that is homologous to its own genomic RNA and the DNA strands are then integrated into chromosomes of host cells. Thereafter, the viral information is perpetuated by cell division and the immune response to infection is not able to effect a virus clearance. Although complete BLV particles are not produced in vivo, they can be readily demonstrated in vitro by their ability to induce the formation of syncytia in cell cultures. This type of assay has been used to show that the BLV genome is carried by lymphocytes, especially those in the peripheral circulation.

How is infection diagnosed?

Although syncytium induction assays detect infectious BLV, they are not simple to perform. Therefore the routine diagnosis of infection is made by a serologic test which detects antibody to a glycoprotein antigen that is found on the surface of virus particles and on the cytoplasmic membrane of infected cells. The most commonly used tests are: agar gel immunodiffusion (AGID), radioimmunoassay, enzyme-linked immunoassay, and virus neutralization. Although the AGID test is the least sensitive, it is considered sufficiently reliable for most purposes and is the only test currently available in most diagnostic laboratories. In some infected cattle that have very low antibody titers, the AGID test may occasionally give a false negative result. Low titers are most frequently encountered in cattle that have been recently infected (less than 3 months), and in pregnant cows, especially during the last month of gestation and the first week post-parturition. A few other cattle maintain persist-

ently low titers after infection so that in repeated AGID tests they are sometimes positive and sometimes negative. In general, however, once an animal becomes AGID seropositive it remains seropositive for the rest of its life. If the more sensitive tests are used, continual detection of BLV antibody is a certainty. It should be noted that calves that receive passive immunity via colostral antibody will be positive in the serologic tests even though they are probably not infected. By 6 months of age almost all non-infected calves will be negative in the AGID test although the more sensitive tests may detect antibody 2 or 3 months longer.

How is BLV transmitted?

Most BLV infections in cattle are the result of horizontal transmission between unrelated animals. The major source of infectivity is blood. Of course, any secretion that contains a significant number of lymphocytes could also spread the virus, but blood is undoubtedly much more infectious. Because BLV is not released from lymphocytes until they leave the host, transmission requires the direct transfer of living cells. Lymphocytes can remain viable for many days in uncoagulated blood but they will not survive drying or freezing. The exposure of mucous membranes to blood can initiate infection but we believe the most common route of entry is the skin. In this regard, many opportunities for mechanical transfer of blood can be postulated: use of common bleeding needles without adequate cleaning between animals; surgical procedures or trauma which results in significant blood contamination of a premise, ear tagging or similar operations that may result in blood or tissue contamination of instruments, heavy exposure to biting or blood-sucking insects, and the use of nose leads, especially if there is significant damage to nasal mucosa or when an infected animal is producing a copious cellular nasal exudate.

Besides contact transmission, there is also a small proportion of animals that are actually infected at birth as a result of in utero infection from the dam. Various studies indicate that 3 to 25% of the calves that are born to BLV-seropositive cows acquire infection in this way.

Another possible source of infectivity is the lymphocytes that are present in colostrum or milk. Calves that nurse infected cows are usually protected because the colostrum they receive also contains virus-specific antibody. Calves from negative cows don't receive this protection, however, and they can become infected if they are fed milk from a positive cow.

There have been a large number of studies examing the potential role of semen in spreading BLV. Results of these experiments indicate that there is virtually no risk in using semen from BLV-positive bulls for artificial insemination. In natural service, of course, such animals would have to be considered possible sources of virus transmission via contact exposure.

How often does BLV produce clinical disease?

After the serologic tests were available, it became clear that only about one-third of the BLV-infected cattle develop persistent lymphocytosis. This finding led to a totally new perspective on the relative prevalence of infection and the incidence of disease. One of the most thorough examinations of BLV oncogenicity in a large cattle population showed that the annual death loss from leukosis represented only about 0.4% of the cattle that were actually infected with BLV. Even in a herd that is genetically predisposed to tumor development, it has been found that less than 5% of the infected cattle will develop a tumor.

Genetic influence is believed to play a significant role in the pathogenesis from BLV infection to tumor. There are many examples of unusually high tumor rates in some herds, in certain cow families, and sometimes in the offspring of particular bulls. Besides genetics, there may also be management factors that can affect the number of tumor cases that are observed. For example, because enzootic bovine leukosis is a disease of older animals, a herd with a high average age might be expected to experience more tumor loss than one which does not retain older cattle (assuming the same BLV prevalence in both herds). It is also possible that there are different strains of BLV with varying degrees of oncogenic potential, but as yet there is no evidence that this situation exists.

Although many other RNA tumor viruses can produce severe clinical effects that are unrelated to their oncogenicity, such as immunosuppression, reproductive failure, etc., all studies to date have failed to show that this type of activity is characteristic of BLV. Within an individual herd there does not appear to be any correlation between seropositive status and poor milk production, infertility, or an increased culling rate due to other disease.

What is the economic impact of BLV in the United States?

It is difficult to assess the losses from bovine leukosis because it is not a reportable disease, but some estimate of the problem can be obtained from federal meat inspection reports. From 1957 to 1974 the number of condemnations for lymphosarcoma (adult type) ranged from 15 to 19 per 100,000 cattle slaughtered. In 1975 and 1976 there was a sharp decrease but since then the number of condemnations has risen continuously to 27 per 100,000 in 1981. We suspect that these recent fluctuations may reflect the influence of market beef prices and/or milk market orders on the type (beef or dairy) and age of animals being slaughtered. Production type influences tumor rate because in a given geographic region the prevalence of BLV infection is usually much higher in dairy than in beef cattle.

In addition to carcass condemnations, there are also many lymphosarcoma deaths on the farm. A Minnesota study found that only about one-half of the cases diagnosed by veterinarians go to slaughter. If we assume this is representative of the country, we can estimate that in 1981 there were approximately 18,000 cases of leukosis caused by BLV in the United States.

Besides death, another, and perhaps more significant, loss

from BLV results from the export restrictions that apply to infected cattle. Because some countries in Europe have had long-standing leukosis control programs, they are understandably reluctant to allow the importation of infected cattle, and other nations, even those where BLV is already endemic, have pursued similar policies. Futhermore, there recently has been an increased awareness of BLV among producers in the United States, which occasionally results in similar problems involving domestic sales.

The main reason BLV has so much economic impact on sales is that the virus is reasonably prevalent in the United States. In testing of serums submitted to a federal laboratory for export certifications, rejection rates because of BLV reactivity ranged from 12 to 19% during the past 6 years. Serologic surveys from various parts of the country showed that 13 to 48% of the dairy and 14 to 19% of the beef cattle were infected.

In addition to tumor losses and interference with sales income, another economic consideration of BLV is the potential for an adverse consumer reaction to presence of the virus in our meat and milk supply. Numerous epidemiologic, serologic, and virologic investigations have failed to provide any evidence of a relationship between BLV and human maligniancy. However, negative findings are always open to question as new techniques, new understandings of molecular biology, etc., are developed. Therefore, it is not surprising that many scientists are relunctant to state with absolute certainty that there is no reason to be concerned, even though all available data lead to such a conclusion.

How can BLV be controlled?

The earliest efforts to control leukosis resulted from governmental policies that were developed in Denmark and Germany 20 to 25 years ago. These programs used the test for persistent lymphocytosis to identify infected animals and required either slaughter of all affected individuals and their progeny or the complete disposal of all affected herds. Both methods markedly reduced tumor losses and when serology replaced hematology, the programs also quickly resulted in virtual eradication of BLV. Workers in several other countries have reported similar successful applications of test and slaughter regimens in test herds. Although testing protocols vary somewhat in minor details, the general principles are as follows: all cattle are tested with the AGID test, reactors are removed as quickly as possible, and testing is repeated 4 to 6 months later. In more than 90% of the herds, BLV is permanently eradicated after only 2 tests, but in a few instances reactors have been found as long as 2 to 3 years after initiation of the program.

In many herds, especially those with a high prevalence of infection, culling of all reactors cannot be economically justified. It is possible in such herds to separate the infected cattle from the rest of the herd and thereby severely limit, if not totally prevent, spread of the virus. Even though only minimal separation is required, however, such a program frequently presents considerable management problems, especially in dairy herds for which only a single milking facility is available.

For herdsmen that are primarily interested in raising young BLV-free animals for domestic sale or international trade, there are several options for the rearing of such calves. The most effective approach is to select only calves from seronegative cows and then raise them as an isolated group. If it is necessary to select calves from positive cows, they can be fed colostrum from seronegative cows and tested as soon as possible. This method requires considerable effort, however, and it is easier to wait until colostral antibody is gone and then test to find out which calves are infected. It should be recognized that the latent period of BLV sometimes can be quite long and the virus-free status of calves from infected dams is never as certain as calves that are taken from non-infected dams and raised in isolation.

Another possible approach for obtaining BLV-free calves from a high-prevalence herd is to use embryo transfer into negative recipient cows. Preliminary trials indicate that this technique would be highly successful but there may be some question as to its relative cost compared to the calf management procedures described above.

There have been only a few limited attempts to prevent BLV infection by immunization with a killed virus vaccine. Although such a product appears to be biologically effective, its usefulness would probably be quite limited because vaccinated cattle would very likely not be accepted in international trade.

References

1. Bendixen, H.J., 1965. Bovine enzootic leukosis. Adv. Vet. Sci. Comp. Med. 10:129-204. 2. Burny, A., Bruck, C., Chantrenne, H., Cleuter, Y., Dekegel, D., Ghysdael, J., Kettmann, R., Leclercq, M., Leunen, J., Mammerickx, M. and Portetelle, D., 1980. Bovine leukemia virus: Molecular biology and epidemiology. In: G. Klein (Ed.), Viral Oncology. Raven Press, New York, pp 231-289. 3. Burridge, M.J., 1981. The zoonotic potential of bovine leukemia virus. Vet. Res. Comm. 5:117-126. 4. Ferrer, J.F., 1980. Bovine lymphosarcoma. Adv. Vet. Sci. Comp. Med. 24:1-68. 5. Miller, J.M. and Van Der Maaten, M.J., 1982. Bovine leukosis—its importance to the dairy industry in the United States. J. Dairy Sci. 65:2194-2203. 6. Mussgay, M., Dietzschold, B., Lorenz, R., Matheka, H.D., Matthaeus, W., Straub, O.C., Weiland, F., Wilesmith, J.W., Frenzel, B. and Kaaden, O.R., 1980. Some properties of bovine leukemia virus, its use in seroepidemiological studies, and eradication of the disease from infected herds. Cold Spring Harbor Conferences on Cell Proliferation, 7:911-925. 7. Stober, M., 1981. The clinical picture of the enzootic and sporadic forms of bovine leukosis. Bov. Pract. 16:119-129. 8. Straub, O.C., 1981. Enzootic bovine leukosis. In: E.P.J. Gibbs (Ed.), Virus Diseases of Food Animals, Volume 1, International Perspectives. Academic Press, New York, pp 683-718. 9. Van Der Maaten, M.J. and Miller, J.M., 1979. Apprasisal of control measures for bovine leukosis. J. Amer. Vet. Med. Assoc. 175:1287-1290.