Bovine leukemia virus: between animal production and human health

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Bovine leukemia virus (BLV) is a retrovirus of the deltaretrovirus genus, infecting B lymphocytes and generating polyclonal expansion. In ruminants, it integrates as a provirus into the host’s genome and generates a lifelong infection throughout its life. According to the World Organization for Animal Health (WOAH), it is a disease of international importance for the animal trade (1). It is known as the significant neoplastic disease of cattle and is one of the five most critical viral agents in livestock production (2,3).

BLV affects the health of animals and produces economic losses in the livestock industry (4). BLV is genetically related to human T-cell leukemia virus types 1 and 2 (HTLV-1 and -2) and simian T-cell leukemia viruses (STLV) (2). Approximately 70% of infected cattle are asymptomatic during their life. 30% of cattle present an abnormal proliferation of B lymphocytes known as Persistent Lymphocytosis (PL). In the most advanced stages of infection, 1%-5% develop B-cell lymphosarcoma in lymph nodes and other organs. Therefore, the disease is characterized as a chronic pathology called Enzootic Bovine Leukosis (EBL) (5,6).

EBL is endemic worldwide, and programs to eradicate the infection are considered a challenge. Most European Union countries have successfully eradicated EBL by using laboratory diagnostic tests and identifying infected individuals for elimination from the herd (7).

The Americas have the highest prevalence in the world (Figure 1). The global prevalence is between 5-90%, in Turkey 2.3%, 3.9% in Mongolia, 9.7% in the Philippines, 12.6% in South Africa, 21.5% in Egypt, 41.3% in Iran and 68.1% in Japan (4,6).

BLV is present in circulating lymphocytes in the peripheral blood of infected animals, and transmission occurs primarily by transferring infected cells through blood and fluids to another host (1). Horizontal transmission generally occurs iatrogenically through direct contact through blood transfusion, shared needles, and transrectal palpation; insect transmission has also been reported. Vertical transmission is possible prenatally in the uterus and during lactation through colostrum or infected milk (1,8).
Natural BLV infection is not limited to cattle. Although BLV can infect other species with shorter latency periods, buffaloes, sheep, goats, yacks, and alpacas are susceptible (9). In these species, the ability of BLV to induce lymphoma has been reported both in vitro and in vivo (7). The presence of the virus in different species makes it challenging to implement prevention and control strategies in livestock farming (6).

BLV viral RNA is reverse-transcribed into double-stranded DNA, and proviral DNA molecules are synthesized. Regulatory proteins command viral transcription and nuclear export of the provirus to the cytoplasm. The genetic material is integrated into the genome by inserting at random sites in the nucleus of infected host cells. The virus manages to establish a lifelong infection, even in the absence of detectable BLV antibodies (10).

Regarding pathogenesis, when the infected cell integrated with the BLV provirus is transmitted to a new host, the provirus is expressed as viral particles that infect immune system cells. BLV has a particular affinity for circulating B lymphocytes in the peripheral blood of infected cattle and, to a lesser extent, in T cells. During infection, the virus interferes with gene expression and the cell signaling cascade, altering proliferative and apoptotic responses. In the latency period, viral transcription is blocked.
Cattle that present LP trigger a massive proliferation of B lymphocytes that express Ig and CD5+ antigens on their surface by blocking their apoptosis instead of triggering their proliferation (2). The pathogenesis mechanisms of BLV that change the latency period and generate the emergence of EBL are unclear. However, it is believed to occur through the deregulation of several signaling pathways and the expression of genes that encode Tax proteins, BLV mRNA, antisense RNA, and microRNA (4).

The lack of information on the impact of BLV in cattle is probably due to the low percentage of animals that develop lymphoma (11). However, studies show that infected animals maintain increased CD5+ and IgM+ B cells circulating in the blood (10). This triggers abnormal immune function, causing adverse effects on the immune response to vaccines and infections. These alterations reduce milk production, favor an increase in infectious diseases in livestock (11), and decrease the lifespan of infected animals, a decrease in carcass weight, and sanitary restrictions for their marketing (12).

Throughout the world, programs to control and eradicate BLV infection are considered an economic and health challenge (2). In order to reduce economic and food losses, it is crucial to identify livestock with high viremia (12). According to WOAH, diagnosis is based on antibody detection tests such as agar gel immunodiffusion and ELISA. Virus culture and detection of the BLV provirus by sequencing are also diagnostic techniques (13).

Concerning immunoprevention, work has been conducted to develop a vaccine that permanently stimulates viral factors to achieve an adequate host immune response. There is a recombinant vaccine using two phenotypically attenuated strains but with the capacity to maintain the structural genes for replication. The results showed fewer replications than the natural BLV strain and a persistent response against anti-BLV antibodies. Currently, the challenges are increasing prevention and making the vaccine available to livestock farmers (14).

On the other hand, the transmission of BLV to humans has spread over the years. BLV proviral DNA fragments have been found in breast tissues, blood samples, and human sera in the United States, Brazil, Australia, and Iran (15). In Colombia, the sequence of the virus obtained from the breast tissues of women and the meat and milk of cattle from a region of the country was analyzed (6). The circulation of haplotypes was identified in women and bovine meat and milk. Shared sequences of haplotypes 1 and 4 were identified, suggesting cocirculation between cattle and humans (6). 95% identity was determined in the sequences, with more significant evidence of haplotypes in the female samples (6).

The circulation of haplotypes between the animal-human interface also supports the hypothesis of transmission routes in the same ecological niche through food as a means of dissemination to humans (3). Also, the involvement of BLV in tumor formation has been determined. The virus was correlated with breast cancer, with a prevalence of 26.8% in women in Pakistan, with a statistically positive association (odds ratio = 0.3889; confidence interval = 1.18; p = 0.0029) (16). In contrast, no evidence of proviral DNA or antibodies was found in human specimens in Japan. This finding is curious since Japan has a high prevalence in its herds of 68.1% (16). However, it is possible to associate it with the low average consumption of bovine meat and milk, in contrast to Pakistan, which has a high consumption of raw milk. It is essential to continue research on variability in developing immune responses in different human populations, considering social and cultural factors that influence transmission (15,16).

In conclusion, the prevalence of the virus and the subclinical presentation of BLV have increased in endemic countries, mainly in Latin America. The current challenges consist of prioritizing veterinary health systems emphasizing an excellent diagnosis to carry out effective prevention and early control of BLV. Finally, we must continue investigating the possible zoonotic potential of BLV, the transmission routes to humans, and its association with breast cancer. In the future, BLV may be considered a zoonosis.
REFERENCES


