

Bovine Leukemia: Zoonosis Associated with Breast Cancer in Humans?

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Abstract

Bovine leukemia virus (BLV) is the causative agent of enzootic bovine leukemia. It is proposed that BLV is restricted to bovines, but there are some reports of its presence in humans and its possible relationship with breast cancer. Considering that any relation or association between this virus and breast cancer could be relevant to human public health and to cattle producers worldwide, it is crucial that several research groups keep investigating in the topic with the aim of confirming the role that this virus should have in breast cancer development. Due to the lack of a vaccine, prevention and control strategies should be implemented by governments where livestock is rising.

Keywords: Breast cancer; Bovine leukemia virus; Viral tropism; Cancer association

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Bovine leukemia is a disease reported by Leisering in 1871, associated with bovine cattle. Leisering identified in some of the animals with this disease, the development of splenomegaly and persistent lymphocytosis while most of them remain asymptomatic [1,2]. Furthermore, it was noticed that the presence of this disease could lead to important economic losses to dairy and meat herds, as well as dual-purpose bovine herds, due to the fact that milk production and weight development are affected. In addition, infected animals become susceptible to acquiring secondary infections what decreases their health conditions and thus their expected production yield [3,4].

Later on, in 1969, Miller and co-workers identified the associated pathogen to the disease, which is known nowadays as the Bovine Leukemia Virus (BLV). Afterward, it was described as an enveloped retrovirus, with a size between 80-125 nm. It is classified as a deltaretrovirus, belonging to Retroviridae family, Orthoretrovirinae subfamily. In this group, are also classified HTLVs, viruses related with neoplastic processes in humans [5]. Together with other retroviruses, their viral genome is a bicatenary RNA with positive sense polarity. It has 3 main Open Reading Frames (ORFs), which encode gag, env and pol genes with 2 Long Terminal Regions (LTRs) at the beginning and the end of the genome. In addition, it has a pX region, which has the information for auxiliary proteins for regulatory purposes such as Rex and Tax proteins, who seem to be associated with carcinogenesis process [6,7].

Until now, viral tropism has been described by the infection of B-lymphocytes as target cells in bovine cattle. However, there are some other reports that show the ability of this virus to infect different kinds of cells likewise induce damage and alterations in some other different species [8-11]. In 1984, Kettman and his group established the possibility that BLV could infect hosts like sheep, chicken, and goats, what was proven by inducing infection with in vivo assays, where, as a result, was obtained the induction of damage as it occurs in bovines [8,11]. Another important approach was performed by Levkut and co-

workers who infected rabbits with the virus, and obtained clinical manifestations related to encephalitis; authors suggested that it could be understood as a zoonosis process influenced by the presence of the virus [12].

Some viruses, basically those with DNA genome as well as retroviruses, have been ascribed to the development of cancer in humans. For instance, Papillomavirus has been related to cervix cancer, Epstein-Barr virus with Burkitt lymphoma, Hepatitis B and C virus with liver cancer and HTLVs with leukemia in humans [13,14].

The relationship between virus and cancer has a long history. Some Nobel Prizes have been awarded to researchers who worked on this issue, for example: Peyton Rous was awarded in 1966 for the sarcoma virus in chickens; David Baltimore and Howard M. Temin received the prize in 1975 for their discovery of reverse transcriptase; and J. Michael Bishop and Harold E. Varmus in 1989 were honored for demonstrating that retroviral oncogenes derived from cellular genes in the host in 1976 [15].

Since then, animal and human cancers have been associated with a viral etiology in most of the cases. One of the most important examples of this association is the case of MMTV and mammary cancer development in mice, where it is established that the virus could infect directly the mammary gland, induce cellular alteration and is transmitted to progeny through the milk [16]. In further studies, another important proposal about this virus is that besides the development of breast cancer in mice, it could be also involved in the development of breast cancer and lymphomas in human beings [17,18]. Even though, there is not enough evidence of causation and a lot of controversies are still reported in the literature about this issue, what implies that future research is needed to be performed [19].

Breast cancer in humans is still one of the pathologies with highest numbers in morbidity and mortality rates worldwide [20,21], by the way, its prevalence is considerably higher in regions with frequent consumption of red meat and dairy products derived from bovine cattle [22-25]. High prevalence of breast cancer in meat-consumption countries and the fact that probably viral tropism is not exclusive to bovines, led to some researchers to seek for the presence of BLV in humans [26]; in order to know if this virus could be involved in the breast cancer development, with some hypothesis such as that it could

be infecting human cells, inducing genotypic alterations related with cellular transformation, and thus, probably having a relationship with tumor genesis in humans.

With this perspective, Dr. Buehring and co-workers' group, in the University of California, Berkeley, have performed some studies related to this topic. Their first approach was published in 2003, where they looked for antibodies in 257 human serums against the p24 viral protein, in this first study they found reactivity in 74% of the analyzed samples [26]; although the antibodies reacted against the virus, for the authors was not clear at all if the virus could be infecting humans or could be a reaction just for the viral entrance, though, authors suggested that a complete viral cycle could be occurring in humans cells due to the immunological response, but further studies are needed to clarify this concern.

Afterward, Ochoa and coworkers in Colombia [27], looked for the presence of the virus on ductal carcinoma samples, where they found that 4 out of 56 samples were positive for gp51 viral antigen in tumoral cells. In a subsequent study, this group determined the presence of a segment of the gag gene of the virus (380 pb) in human mammary tissue, with and without a cancer diagnosis [28]. As a result, authors reported the presence of the gene segment of the virus in a 40.5% of a total of 106 samples, including positive and negative cancer tissues. Particularly, authors reported that from samples with the presence of the virus, 36% belonged to positive cancer samples and 45.2% belonged to of negative cancer samples, where authors could not conclude if BLV is really associated with breast cancer development, but brings up new questions and doubts about why is there a bovine virus present in humans and if it could be influencing the development of cancer.

Last advances of Dr. Buehring's research, are trying to highly associate the presence of the virus with the development of breast cancer. In 2014, authors reported the presence of tax gene in 97 human samples for 217 samples included in the study, what raises concerns about a risk of infection of this virus to humans, and that it could be involved in the breast cancer development [29]. In her last report [30], authors established that the exposure to BLV is an important risk factor that could be highly associated with breast cancer development, with this in mind, it is important to clarify that further studies are needed with the aim of establishing a relation between the virus and the disease.

In concordance with the previous findings, the hypothesis that BLV is related to breast cancer has been formulated for a while and is getting stronger. Even though, it remains the doubt about if the virus causes cancer, is associated with cancer or just if the presence of the virus is related with the presence of the disease but without any influence in the process.

So far, although it is known that this virus causes problems in bovine public health, issues such as the difficulty of generating vaccines and the amount of asymptomatic infected animals, have been taken place to underestimate the importance of this virus by government entities and cattle keepers, until the point of having few countries with mandatory notification for this disease.

By the way, taking into account that the lack of the vaccine, as well as a specific treatment for the disease, it is necessary to include Control and Prevention strategies within farms and herds such as separating infected animals from herds, improving processes of disinfection, avoid sharing working tools or food for cattle and where possible, carry out serological diagnosis for cattle farms; together with

abstaining from selling infected animals trying to control the spread of the virus and to decrease the tentative infection in humans [31].

Prevention strategies and proposals for further studies to inquire which kind of relationship this virus has with breast cancer should be executed to determine if BLV could be defined as a zoonosis associated with cancer development. Nevertheless, it is important to remind the proposals made by Joshi et al. to strongly associate causation of a virus with breast cancer [32,33]:

- The presence of viral markers: Should be evaluated in cases and controls studies, where the presence of viral markers should be greater in cases groups than in controls of the same geographic region.
- There should be a temporal relationship; virus exposure should occur before illness development.
- Association with the virus should be proven by different investigators
- Prevalence of the virus should be higher in prevalent breast cancer geographic regions
- Exposure to the virus and incidence of breast cancer should be related
- There should be a connection between transmission mode and natural course of the disease
- Oncogenic capability for the virus should be demonstrated, related with infection and transformation properties of mammary epithelial cells and causing malignancy in animal models
- Prevention of infection and spread control of the virus should decrease breast cancer incidence

Currently, our research group is working in the presence of gene segments of the virus in breast tissue samples as well as in blood, milk and meat of bovine cattle trying to elucidate any relationship between circulating strains in Colombia with the infection in humans.

As a conclusion, there has been increasing the shreds of evidence suggesting that it could be an important relationship between the presence of the virus and the breast cancer. However, even stronger findings are needed to remark this affirmation. If there would be any association, it would provide important impact in the social, economic and political field worldwide, mostly in countries with high livestock development.

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