

## A Role for the Measles Virus in Oncology

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Classic Hodgkin lymphoma (CHL) stands out among malignant tumors, by a relative scarcity of the tumor cells in the involved lymph nodes. These Hodgkin and Reed-Sternberg (H/RS) cells are distributed unevenly in the lymph node sections, within a majority of inflammatory cells, fibrosis and necrosis. It is agreed, that independently of the proportion of H/RS cells in CHL, the outcome of the malignancy will be favorable, with a cure rate of 75-90%. Such a therapeutic achievement is unusual for cancer at large.

When considering the many prognostic and risk factors related with CHL, the stage of the tumor, is, as expected, the most relevant. Evidence of systemic symptoms: fever above 38 °C for at least a month; weight loss of more than 10% of the body weight, lasting six months or more and/or drenching night sweats for a month, alone or collectively, worsens the prognosis. A difference is described between genders, females faring, as a rule, better than males, no consideration being given to a higher incidence of nodular sclerosis CHL in females. Indeed, children and older adult males with mixed cellularity CHL, especially from developing countries, get on worse with the diseases. In contrast, females tend to be included in the bulk of CHL patients, those aged 15-36, with a favorable disease.

Some 15-20% of human cancers are thought to arise by mechanisms which relate with viruses, bacteria or parasites. Proof for their involvement comes partly from the detection of the micro-organism in biopsies and partly from epidemiological and animal investigations. Viruses might alter cellular genes directly contact with RNA tumor viruses, or may affect cell proliferation, as with DNA tumor viruses, and thus contribute to tumors formation. As a procedure, the virus is responsible for only a limited number of steps in the progression of cancer. In most cases, the precise role of a cancer-associated virus is hard to decipher, due to the long delay from the initial virus infection. In any case, the number of human beings infected with the above viruses, is much larger by far from that of patients who develop cancer. So the tumor viruses probably act in conjunction with additional factors.

Chronic inflammation may play major role in the above processes as well as in other pathologic events which may lead to cancer. In some cases of unresolved chronic inflammation, the immune response becomes maladaptive, hence promoting tumorigenesis. A regenerative process supported by an group of bioactive mediators, helps cell survival, tissue remodeling and angiogenesis. The mediators will also cause genomic stress and mutations. A correlation between CHL and the Epstein-Barr virus (EBV) has been demonstrated many years ago, with a causal relationship being established as soon as 2001. The incidence of Epstein-Barr virus infection in CHL has shown a wide geographic variation, from 17 to 30% in industrialized places, to as high as 100% in some developing countries. Several further years elapsed before the

distribution of EBV infection occurs by gender, age and CHL type was determined. Thus EBV is expressed more frequently in males, notably in children from developed place as well as in old people all over the globe, these two groups showing as a rule mixed cellularity CHL. The female CHL patients stand out in general, by showing nodular sclerosis CHL with a markedly lower level of EBV expression and a young adult age.

A small subset of young adult males will develop CHL, after recovering from infectious mononucleosis. The EBV is recognized as oncogenic. Mostly, its transforming potential, with cell proliferation, inflammation and apoptosis arrest, has been related to the nuclear factor- $\kappa$ B (NF- $\kappa$ B) and the EBV/LMP1 will further contribute to the inhibition of the H/RS cells apoptosis. As noted, EBV does not play a significant role in the largest subset of CHL, that affecting young adults, and most of the female CHL patients. The above subset, young adult female patients correspond to that defined in classic epidemiological studies in the early 1980's as patients with the "late host response model". These patients are considered to be submitted to a late exposure to a common infectious agent, the term "late" meaning that instead of meeting the common infectious agent for the first time in early childhood, this occurs at adolescence or young adulthood. The epidemiological thesis further suggests that these individuals had a late encounter with the agent, since they had few and late contacts with other children (single child; individual family house). The late host response model, it is the most common agent, probably a virus, reaches the organism for the first time at a stage in which the metabolism and/or the hormonal balance is markedly different from that of a toddler, age at which the encounter regularly takes place. At this point, the internal environment has varied deeply and probably, so does the immune system.

When looking for a substitute for the EBV in CHL, it was observed that none of the additional viruses, once considered as possible candidates, have been detected in CHL tissues. The single virus to be incompletely excluded at that time was the HCMV. However, one distinct virus showed qualities and associations which recalled to various extents those of CHL. The "candidate" proposed is the measles virus (MV). It penetrates the organism through the oropharynx. And since it is lymphotropic, it invades the adjacent lymphoid tissues. This may account for the vast majority of CHL starting in cervical and/or in mediastinal lymph nodes. All the known oncogenic DNA viruses tested in EBV-negative HL cases, showed absence of involvement. Histologically, infection with MV elaborates multinucleated cells - the Warthin-Finkeldey polykaryons. This polykaryons differ largely from the H/RS cells of CHL, mainly by the number of nuclei (up to 70) as well as by their phenotype (they are T-lymphocytes).