

The Measles Virus Expression Correlates with Classical Hodgkin Lymphoma and Other Malignancies. A Short Commentary

Daniel Benharroch*

Department of Pathology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Abstract

We have suggested, several years ago, an association between the measles virus and classical Hodgkin lymphoma. However, this relationship was not accepted by the isolated research groups which dealt with the issue. In this short commentary, we recall the traits of the virus which were suggestive of a familiarity with Hodgkin lymphoma. We mention, in addition, older articles which highlight these similarities. As the impact of apoptosis in Hodgkin lymphoma is controversial, a chapter is saved for it. Atypical measles syndrome has long been forgotten. It is mentioned in the present context. The consensus agrees that immunity waning is not a significant factor regarding the measles virus. Is it indeed?

Keywords: Classical hodgkin lymphoma; Measles virus; RNA; Immunohistochemistry; Apoptosis

Introduction

In 2004, we reported on data which, we assumed, supported an association between classical Hodgkin lymphoma (cHL) and the measles virus (MV). This was based on the MV proteins by immunostaining and on MV-RNA expression, by RT-PCR and *in situ* hybridization [1].

In 2007, two European research groups rejected our thesis [2,3], on the ground of a methodology more sophisticated, but much more selective than ours [2]. One group [3] even specifically singled out patients with a past history of measles, mainly in childhood.

We therefore understood that there was room for further establishment of our hypothesis. We then demonstrated a relationship between the MV expression and various solid tumors [4-6]. In addition, while revising the role of apoptosis in cHL, it became clear to us that the MV, as some of the other viruses, may modulate the infected cell apoptotic apparatus. It was suggested that apoptosis might represent one of the mechanisms used by the MV to regulate the B-cell lymphocyte in its process of transformation.

In this short commentary, I will recall the original reasons which suggested to us the adoption of the MV, as a possible additional factor in the pathogenesis of cHL [1,7]. Previously published data, will be reviewed, which sustains the MV as a probable causative factor in cHL [8-15]. Next, apoptosis will be elaborated on, as a further support of a mechanism active in the transformation of the B-cell lymphocyte. A brief mention will then be made of the atypical measles syndrome, as a possible player in this occurrence. The role of the universal, two dose measles vaccination and the eventuality of immunity waning will be mentioned. Last, the confirmation of a role played by the MV, apoptosis regulation and CD15 expression, in lymphomagenesis, especially concerning the features of lymphangiogenesis, will be discussed.

The measles virus may be related with classical Hodgkin lymphoma

The original suggestion that the MV may play a role in cHL was based on several of this virus feature [1,7]. First, the MV is a lymphotropic virus, and by getting access to the organism through the upper airways, will spread predominantly to the cervical and mediastinal lymph nodes. In addition, the acute measles infectious diseases, is usually complicated by a short-lived (of about six months duration) cellular

immune deficiency, irrespective of the life-long specific protective immunity. A striking histopathologic feature in measles is the presence of polykaryons in the infected tissues. Last, following the routine use of the MV vaccination, since 1963, measles occurs more frequently after age 5 [7].

These features of the MV looked sufficient for the performance of further investigations. We first carried out immunohistochemical studies, using several experimental and commercial anti-MV antibodies. These studies showed the presence of MV proteins in about half of our cHL cases.

In 2004, we published a study on the probable association of the MV with cHL. This was established on immunohistochemistry, on RT-PCR and ISH.

Archival supporting articles

Our findings regarding the relationship between MV expression and cHL, as well as with several solid tumors, are sustained by numerous previous publications. Thus, the findings were consistent with random cHL regression following MV vaccination or measles infection [10-13]. Moreover, reports of central nervous system tumors and cHL, followed exposure to MV around birth [8,9]. Last, childhood viral infections, including measles, may protect from the development of cHL [14].

A marked rise in the occurrence of HL in young adults in Israel may be associated with the waning of the immunity, following the universal two-steps anti-MV vaccination [16]. However, a significant waning has not been proven. Another aspect of this issue is enhanced by the description of the inhibition of ubiquitination and stabilization of the human ubiquitin E3 ligase, PIRH2 by the MV phosphoprotein [17].

*Corresponding author: Daniel Benharroch, Soroka University Medical Center, 1 Itshak Rager Boulevard, P.O.Box 151, Beer-Sheva 84101, Israel, Tel: +972-507579140; E-mail: dbenharroch@yahoo.com

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The role of apoptosis in classical Hodgkin lymphoma

Before a consensus established a negative role for apoptosis in cHL, we had investigated this issue in two articles. One of them showed morphological and electron microscopic evidence of apoptosis in HL [18]. The other demonstrated the wide spectrum of an apoptotic index [19]. The consensual view stated that since the cHL tumor cells, the Hodgkin-Reed-Sternberg cells, lacked the capacity to express the BCR on their cell membranes, they should undergo apoptosis. Their survival is suggested to be due to NF- κ B activation, which together with the overexpression of LMP1/EBV generates resistance to apoptosis.

In spite of the difficulty in demonstrating the activation of the apoptotic apparatus by isolated techniques, a wide range of apoptosis was evident in our cHL patients. In a later revision of the issue, we confirmed that in only 55% of an expanded cohort (217) of cHL patients, we found evidence of apoptosis inhibition [20]. An unexpected finding of this revision, was a significant association of the apoptotic index with the expression of the MV in cHL tumor cells [20]. Moreover, we found that the classical NF- κ B did not correlate with apoptosis arrest in our patients. Of note is the finding that measles virus V protein may bind to p65 (RelA), to suppress NF- κ B activation [21].

The measles virus may therefore be involved in the cHL pathogenesis, by regulating the infected cell apoptosis, perhaps in conjunction with the stabilization and conservation of PIRH2 [17,20,22,23]. Moreover, it may regulate some of the NF- κ B pathways.

The suggested contribution of atypical measles syndrome

The major aspects of atypical measles syndrome (AMS), which may contribute to the association of MV with malignancies, are the waning of the specific immunity and a secondary exposure to wild-type MV.

The AMS was described in the context of a formalin-inactivated anti-MV vaccine, applied in 1963, but banned in 1967. The syndrome, consisting of fever, skin lesions, pneumonitis, abdominal pain, with transient hepatitis and eosinophilia [24,25] has occurred up to 16 years after the official use of formalin-inactivated anti-MV vaccination [26]. The AMS has still been found to occur to the present day [27,28].

So far, no indication is to be found of an association between AMS and MV-related malignancies. However, this is not surprising, since AMS is not only often missed, but is a condition of which many physicians are not aware. An investigation that would try to disclose the diagnosis of AMS, may uncover further relations between MV and cHL or other malignant tumors.

Although it has never been suggested before, one cannot exclude the possibility that AMS might also be caused by a previous vaccination followed by waning of the specific immunity of a different nature. At this point the several meanings of the "measles paradox" should be mentioned. In a given measles outbreak, some individuals may die and the fatality rate may even be high, while others survive, especially if previously exposed or vaccinated. Susceptibility, as well as resistance to infection is apparently HLA-related. Post-immunization antibody response has been used as a marker of susceptibility. Non-HLA genes have been found in addition to play a role regarding antigen-processing pathways genes, in an independent manner. Thus response to vaccination, may vary in a genetic mode [29]. It has been stated that 3-5% of the population of the USA do not produce an adequate immunity to standard, two dose anti-MV vaccination.

LeBaron et al. [30] examined the eventuality of waning of anti-MV

immunity, in the absence of re-exposure to the wild-type virus. No significant decline of the specific immunity was noted.

An outbreak of measles in New York City in 2011, revealed for the first time transmission of infection from a two-doses vaccinated individual with a secondary vaccine failure. The clinical picture and the laboratory finding of the patient were typical of measles in a never exposed individual. This rare occurrence emphasizes the need for vigilance, independently of the vaccination status [31].

Levine et al. [16] investigated the prevalence of antibodies to MV, in addition to those of the mumps and the rubella viruses in adults, 20 years after the introduction of the 2-dose MMR vaccination in Israel. The 18-19 year-old recruits were examined in 2007. The samples were positive for MV in 85.7% of the soldiers examined, as compared with 95.6% of recruits in 1996. The decline was similar in either sex, irrespective of years of education and of smoking habit, but in Israeli born subjects only. The authors concluded that the last major change in the vaccination policy was responsible for a suboptimal level of seroprevalence. They recommended a supplement to the routine MMR vaccine. They could not identify any of the classical three causes for such an occurrence: suboptimal coverage; absence of natural exposure, though Israel is not particularly exposed and waning immunity, which is not proven for the MV.

Lymphangiogenesis and related features in classical Hodgkin lymphoma

We recently have identified associations between lymphangiogenesis in cHL and roles played by CD15, sialylated and non-sialylated, the measles virus and apoptosis. These findings obtained independently of previous investigations, seem to lend further support to our thesis [unpublished data].

Discussion

A long time has elapsed since we suggested a relationship between the MV and cHL and since two European research groups declined our proposal. We have nevertheless persisted in our line of research and have even enlarged its spectrum to include several epithelial malignancies. We are in the process of adding an epidemiological aspect to our studies.

It is quite surprising that no additional laboratory did indulge in a similar research. Although the present study does not only look arduous, it is indeed!

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