OPEN ACCESS
Freely Available Online

INTERNATIONAL JOURNAL OF NEGATIVE RESULTS
ISSN NO: 2641-9181

Short Communication

DOI : 10.14302/issn.2641-9181.ijnr-18-2195

Is the Measles Virus Indeed Involved in Carcinogenesis? - Commentary

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Abstract

Objectives: An association between the measles virus and Hodgkin lymphoma has been disclosed by our laboratory in Beer-Sheva, starting in 2003. We question the refutation of our study and the absence of interest among experts.

Methodology: It was based on immunohistochemistry with commercial, as well as experimental anti-measles antibodies. It relied also on RT-PCR and *in situ* hybridization evidence of measles virus RNA.

Key results: At this stage (2004), the link between the virus and the lymphoma was essentially descriptive. The first and last response to our challenge appeared in 2007, in the form of doublet articles, in the same issue of a major cancer journal. The two European research groups responding, rejected categorically our findings by proposing different arguments.

Major conclusion: As reservations to these reactions became soon apparent, a series of papers from our laboratory were published. These articles concerned the evidence of a relationship between the measles virus and additional categories of cancers. Different malignancies in which this virus was not expressed at all, were also described. A further study suggested a mechanism by which the measles virus may activate lymphomagenesis in classic Hodgkin lymphoma. To our dismay, and in spite of repeated calls to verify the various results, no further response was obtained from international experts.

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Running Title: Link of the measles virus with cancer?

Keywords: measles virus; classic Hodgkin lymphoma; immunohistochemistry; RT-PCR; in situ hybridization; endometrial cancer; lung cancer; breast cancer

Received: July 02, 2018 **Accepted:** Aug 29, 2018 **Published:** Aug 30, 2018

Editor: Anoja Priyadarshani Attanayake, Senior Lecturer in Biochemistry, Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Sri Lanka.

Introduction

A hypothesis has been presented in 2004, supporting a role in cancer, for the measles virus (MV), a virus which had not been considered to date as carcinogenic [1, 2].

In this paper, we present an overview of our endeavour for the recognition of a common virus, as the heart of malignancies, to which it had not been associated until now. The thesis further suggests a role for the virus in oncomodulation, in a manner which evokes the controversial effect of the cytomegalovirus in glioblastoma [3].

However, the main issue is that the hypothesis has been rejected by two major groups of scientists in cooperation [4, 5]. But no one else has been motivated to look independently into this question, so far.

Experimental Procedure

A commentary is presented.

Measles Virus and Classic Hodgkin Lymphoma

In 2004, we revealed a link between classic Hodgkin lymphoma (cHL) and the measles virus (MV), using immunophenotyping and several anti-MV antibodies. Of 154 cHL biopsies, 82 were positive for MV antigens (54%)[1]. The association was disclosed to a more modest degree, on the RNA extracted mainly from snap-frozen tissues [4 of 15 hemagglutinin (HA) and 2 of 16 nucleoproteins (NP) MV-RNAs were positive by RT-PCR]. Two of 7 HA and 8 of 21 NP MV-RNAs were equally positive by *in situ* hybridization (*ISH)* [1].

The expression of the MV antigens was evaluated in a clinicopathological association. Positive expression of MV favored female patients (p=0.036), nodular sclerosis cHL (p=0.0013) and early stages of the lymphoma. However, overall, MV-positive expression seemed to be related to a worse prognosis [1].

Reservations

Maggio et al, from Essen, Germany rejected our findings. They were highly selective in their study, and chose 18 of their original 44 snap-frozen cHL tissues, as well as 7 of our 22 cases. The RNAs had to be of a very high quality and the HRS cells chosen had a near perfect morphology. These cells were obtained in single cell microdissection [4]. The 25 selected cases which were submitted to RT-PCR with three primers, were all negative for MV-RNA. By using the GAPDH housekeeper gene, the samples were found to be very rich in RNA [4].

Wilson et al, from Glasgow, UK, refuted also our results [5]. A high proportion of their patients had suffered from measles mostly in childhood. Their immunophenotypic study, in addition, was based on a single commercial antibody, the NP-MV, clone 49-21 (Immunological Direct, Oxford, UK). All their cases were also negative for MV-RNA, by RT-PCR [5].

Our Response

The striking selection employed in Germany, as mentioned above, may have led a bias in the analysis. Our use of a non-selected cohort of cHL patients had pointed out at a low-abundance of MV-RNA, which may be due in part to a long shelf time of the deep-frozen tissues, but also in part to the often numerous ribonuclease-rich eosinophils content in cHL. Thus GAPDH might not be an adequate housekeeping gene in these experiments [6]. Regarding the seven israeli cases found to be negative at examination in Germany, they had been positive in our lab for MV antigens. However, upon RT-PCR or *ISH,* five of them were negative or very weak.

On the other hand, a large part of the Scottish cohort had suffered from acute measles, mainly as children. This is not in agreement with the concept of the late host response model, which suggests that these patients might be protected from the development of cHL [5, 7].

Moreover, using the clone 49-21 (anti-MV-antibody), but this once from Argene-Biosoft, France (#11-045), more than half of our cases were positive for the MV antigen [8].

Our More Recent Findings

Seventy-two percent of our 49 endometrial carcinoma cases were positive for MV antigens in the tumor cells. Using *ISH*, 16/21 cases were positive for MV-RNA. This MV expression was related to a higher mortality rate [9].

In the 65 non-small cell carcinomas of lung studied, 54 were positive for MV proteins [10].

With regard to the 131 cases of invasive ductal carcinomas examined, 64% were positive for MV

antigens [11].

In contrast, the non-Hodgkin lymphomas studied did not express MV antigens, except for the ALK-positive anaplastic large cell lymphoma. Of equally negative MV expression, were seminomas, glioblastomas and mesotheliomas [8].

A second look at the apoptotic status in cHL (apoptotic index) disclosed that, as expected, apoptosis was inhibited in this lymphoma, but that the hindrance was found in 55% of the 217 cases studied only. It is proposed therefore that the MV might regulate cHL via modulation of apoptosis in the tumor cells [12].

Discussion

A role for the MV has been hypothesized by us in cHL, role which *a priori* should not have been played by this virus at all. Of note, the MV has never been considered as oncogenic [1]. Therefore, it is not surprising that scientists, less enthusiast than we were, regarding our hypothesis, might be at least sceptical about our findings. Then, rejection of our thesis occurred. Published in the International Journal of Cancer as doublet articles, the response from Germany and Scotland is very impressive. The repute of the leaders of these laboratories, is remarkable. It might have been natural after reading their comments, to agree with the "sentence" and to step out. In fact, some of the more central figures in our group did just that: they dropped out. However, others did not give up and looked for weaknesses in the apparently powerful refutation. And indeed, we discerned several critical flaws. Ever since the rejection, we have realized that a relevant epidemiological investigation, might be necessary to confirm our data. We turned to several epidemiologists in this country and abroad, but in vain.

The situation today may lean in favour of our thesis, as we have carried on with our research and are still publishing in this domain. However, due to the seniority of the retractors, we still have serious doubts regarding the validity of our data. This is why, we call, once again for the international scientific community reappraisal of our work, as well as for attempts at the reproduction of our research by other investigators.

Conclusion

We are searching for new means of bringing our work to the attention of the experts.

Acknowledgements

We thank kibbutz Sde-Boker for their support.

Conflicts of Interest

The author declares 'No conflict of interest'.

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