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REVIEW

Relevance of the Measles Virus Expression in Cancer - an Update

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Abstract Evidence of an association between classical Hodgkin lymphoma and the measles virus has previously been presented by our group. Arguments held against our thesis were reevaluated. Substantiation of a relationship between the measles virus and additional solid tumors was submitted. Moreover, a pathogenic pathway was suggested to support a possible contribution of the measles virus to the development of classical Hodgkin lymphoma. We have chosen to exclude a discussion of measles virotherapy, since this carries distinct implications. We now add new evidence regarding the expression of the measles virus phosphoprotein in a few cancers. We also suggest a role in this context for atypical measles syndrome in malignant tumors. Last, we propose a collaboration which may make the best, on the one hand of our cohort of classical Hodgkin lymphoma, half of which carry the measles virus expression in their tumor cells. The planned study will also look into the patients vaccination records and into a previous history of the measles disease. On the other hand, cohorts of patients diagnosed with late onset measles will be assessed for the eventual diagnosis of atypical measles syndrome and will be followed up for the subsequent development of a malignant tumor.

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Introduction

In the years 2003–4, we published evidence for a relationship between classical Hodgkin lymphoma (cHL) and the expression of measles virus (MV) proteins and with that of MV-RNA by reverse transcriptase-polymerase chain reaction and in situ hybridization in lymph node tissues [1]. By then, we had no proof of a causal link between the tumor and the virus.

Three years later, our view on the association between cHL and MV was rejected by two European laboratories [2, 3]. As their methodology and more notably the high selection level and/or the confirmation of a previous exposure to measles used by these scientists differed from ours, we realized that the issue has not been completely clarified. At that point, we looked for analogous relations to those found between cHL and MV in various solid tumors [4–6].

While recapitulating the relation of cHL and MV, we explored apoptosis regulation as a possible mechanism of action for MV in cHL, perhaps a suggestion of a causality association [7].

We have recently inquired into the thesis, suggested by the detractors of our findings, concerning a possible cross-reactivity between the anti-MV antibodies that we had used and an unknown human antigen. A thorough homology search of the measles genome as it relates with the human genome, by two independent observers, did not sustain the theory of cross-reactivity [8, 9].

We hereby include new data related to the association between MV and tumors. A multicenter research program which may add some light onto this issue is suggested.

Original Findings

Considering the link between microbes and cancer in other animals, one is surprised to observe that less than 20 % of human cancers are thought to arise by mechanisms which involve also viruses, bacteria or parasites [10, 11].

The organisms may generate a chronic-type inflammation [9, 12]. In some cases with persistent chronic inflammation, the immune response loses its balance, promoting tumorigenesis [12].

Classical Hodgkin lymphoma (cHL) is a malignant tumor of the immune system. Although it is not frequent, it reaches one of the highest incidence in adults between the ages of 16 and 34. Excellent responses to treatment are obtained with this cancer {80–85 % of patients are cured - [13]}.

An association between cHL and Epstein–Barr virus (EBV) was described several decades ago [1, 13–15]. This link varies from 17 to 30 % in some industrialized countries and up to 100 % in a number of developing countries. Epstein–Barr virus expression varies with gender and also with cHL histological subtype [16, 17].

The pathogenesis of EBV-related cHL evolves around the nuclear factor-κB (NF-κB) activation. However, the alternative and not the canonical pathway seems mainly concerned [18–21].

The largest age-incidence curve related with EBV expression categorizes young adults, with a high proportion of females patients, mostly EBV-negative nodular sclerosis HL. A smaller graph hides within the larger curve and includes young adult males with EBV+ and with previous infectious mononucleosis [22].

Thus EBV+ cases in developed countries may account for less than a quarter of cHL, being especially infrequent in young adult patients. The EBV-negative cHL patients comprise mainly women, who are those most expected, according to elaborate epidemiological studies, to be related to the late host response model of common infectious agents [23–27].

Recent findings, based on a genome-wide association study of cHL and EBV status-defined subgroups, support an etiologically high significance of the EBV status for the classification of cHL. It seems that some aspects of cHL may nevertheless be common to both EBV-positive and EBV-negative patients [28].

In 2002, we raised the possible candidacy of the measles virus (MV) for an association with cHL, mainly in a young adult subset of patients. This link was proposed on the basis of the following traits of the MV: measles virus is lymphotropic; acute measles infection is followed as a rule by a transient cellular immune deficiency, in spite of a life-long protective immunity; polykaryons are evident in the infected tissues; since 1963, following anti-MV vaccination, measles infection has occurred more often after age 5 [29, 30].

We therefore proposed MV as a possible biologic agent related with cHL, at least in young adult patients.

In the study, published in 2004, we analyzed 154 biopsies from untreated cHL patients [1]. Eighty two of the 154 biopsies (54 %) were positive for the expression of two MV antigens or more. As demonstrated by the Southern blot, 4 of 15 hemagglutinin MV-RNAs and 2 of 16 nucleoprotein MV-RNAs were positive. By ISH, 2 of 7 hemagglutinin MV-RNAs and 8 of 21 nucleoprotein MV-RNAs were positive [1].

We found a predominant relationship between MV-positive expression and female patients ($p = .036$), and also with nodular sclerosis in contrast with mixed cellularity cHL subtype ($p = .0013$). CD15 expression was associated with a negative MV expression [1].

A multivariable logistic regression model of prognostic factors with dying of cHL in 89 patients, confirmed that a high tumor stage was an independent prognostic factor. It also showed that MV+/EBV- was a negative independent prognostic factor, OR = 10.05 (95 % CI - .98–103.7, $p = .05$) and that MV−/EBV- was also a negative independent prognostic factor, OR = 15.2 (95 % CI – 1.05-220.3; $p = .04$) [1].

This association found between the presence of MV in cHL sustained epidemiological findings on the incidence of brain and spinal cord tumors as well as of cHL following exposure to MV around the time of birth [31, 32]. Our findings were also compatible with reports on random HL regression after measles infection or vaccination [33–36]. In addition, childhood infections, had been suggested to protect from the occurrence of cHL [37].

In spite of finding more female patients, more nodular sclerosis subtype, and more patients with early stages in cases of MV+ cHL, it surprisingly seems that these patients had a worse prognosis. At this time, our descriptive findings did not allow us to establish causality in the relationship between MV and cHL.

Our limitations of the described work are as follows: in 142 patients of our cohort we could not identify a history of previous measles. Moreover, we did not try, by then, to determine the vaccination status of the patients. The discrepancy between the immunohistochemical and RNA molecular data has been referred in our opinion to the deterioration of the RNA, following many years of deep freezing of the tissues.

Dr. Maggio et al Reservations

In an attempt to confirm or refute our findings, Maggio et al. picked 18 of 44 of their cHL fresh frozen tissues chosen for their very high RNA quality and for their superb Hodgkin-Reed-Sternberg morphology [2]. They used UV-laser beam single cell microdissection. RT-PCR was performed with primers from three MV genes. The 18 German cases did

not show the existence of any of the three viral transcripts. The GAPDH housekeeper gene demonstrated a high content of RNA [2].

Dr. Wilson et al Refutation

Epidemiologically, the paper by Wilson et al. [3] points out at a group of cHL patients, a large proportion of whom revealed previous acute measles infection, mainly in childhood. The immunohistochemical study rested on a single monoclonal antibody to NP-MV, clone 49–21, from Immunological Direct, Oxford, UK. By this method, all their cases were negative for measles. Regarding the RT-PCR, GAPDH was used as the housekeeping gene. Again, none of their 20 cases studied were positive for MV, both by RT-PCR and by qRT-PCR (3).

The Israeli Response

We mailed 22 of our fresh-frozen cHL tissues to Germany, chosen for their positive immunostaining for MV antigens, as requested. However, only 7 were singled out, according to the Maggio et al. stringent criteria mentioned above. The seven cases were found by Maggio et al. to be negative for the various MV transcripts studied [2].

Before renouncing our investigation of MV in cHL, we critically censured the various results. We however admit to our willingness to participate in the publication by Maggio et al. [2].

Our Reservations Regarding the German Experiment

We believe that Maggio et al. were extremely selective in choosing the cases to be included in their study. Besides, it is our experience that cHL tissues show a low abundance of MV-RNA, mainly due to their high content of ribonucleases in eosinophil-rich cHL cases and perhaps to a long shelf time of the deep frozen tissues [13]. As a consequence, GAPDH which demonstrates as a rule abundant RNA in tissues examined is probably an insufficient housekeeping gene for this particular experiment [38, 39]. Moreover our 7 cases contributed to the German experiment were all mixed cellularity cHL and most were EBV+ cases. Of these we had studied 5 cases for MV-RNA, 2 of which were faint and three were negative. In addition, one should be reserved when comparing Israel to Germany regarding measles. In Israel, the population has been subject to frequent outbursts of measles and it has shown a steady increase in the incidence of young adult cHL [40–42].

Finally, the measles virus phosphoprotein has been described as an inhibitor of the ubiquitination and stabilization of hPIRH2, an ubiquitin E3 ligase, one of the regulators of the p53 pathway [43]. This finding may be relevant to a putative role for MV in carcinogenesis.

Reservations on Dr. Wilson et al Criticism

A large part of Wilson et al. patients had suffered from measles disease in childhood. This distribution selected a priori is in contradiction with the research of a possible role of MV in the late host response model [37].

We used the same antibody, clone 49–21, presently distributed by Argene-Biosoft, Varlhes, France (# 11–045) and found that 37 of 72 of our cases were positive (data not shown). As noted previously, the choice of the housekeeping gene should be adapted to the experiment [38, 39].

Measles Virus Association with other Cancers

We studied 49 endometrial carcinomas (EC). Twenty of the 36 patients (72 %) expressed MV antigens in the tumor cells, mainly of EC type I. Sixteen of 21 were positive for MV-RNA by in situ hybridization. When EC type II was related with MV expression, we noted a deeper myometrial invasion and a higher mortality [4].

Lung cancer cells have been found to over-express PIRH2, the ubiquitin E3 ligase, which may inactivate p53 [43]. We described 65 non-small cell lung cancers, fifty four of which were associated with MV antigens. This positive expression is related with older patient age, high PIRH2 expression as well as with improved survival [5]. The expression of MV proteins may signify inhibition of ubiquitination of PIRH2, as mentioned above [43–45].

We also studied 131 cases of invasive ductal carcinoma. Sixty-four percent of these were positive for MV antigens by immunostaining. MV antigens expression was linked with ER ($p = .018$); with Ki-67 < 40 % ($p = .029$); with low or intermediate grade ($p = .037$); with age < 50 ($p = .039$) and with p53 overexpression ($p = .049$) [6].

Measles Virus-Negative Cancers

The 25 non-Hodgkin lymphomas examined by immunohistochemistry in the 2004 study [1] were negative for MV antigens. However, ALK1-positive anaplastic large cell lymphomas usually expressed the MV antigens. Seminomas revealed a high background of staining, but no clear positivity for MV antigens. Glioblastomas and mesotheliomas did not express MV antigens (Ariad S., personal communication).

Table 1 Expression of the measles virus phosphoprotein in lung cancer, by western blot. Comparison with the adjacent normal lung tissue

Lung cancer	Positive (%)	Negative(%)	Normal lung (positive %)
Adenocarcinoma	11 (84.6)	2 (15.4)	12 (83.3)
Squamous cell carcinoma	3 (100)	0	1 (100)
Large cell carcinoma	1 (100)	0	0
Adenocarcinoma in situ	1 (100)	0	0

Does the Measles Virus Play a Role in Cancer?

While reviewing the role of apoptosis in Hodgkin-Reed-Sternberg (HRS) cells of cHL, we found, in spite of contradictory evidence, that HRS cells demonstrated inhibition of apoptosis in 55 % of the 217 studied cases only [7]. Besides, in contrast with the consensus view, it is suggested that NF-κB (p-65) activation and EBV/LMP1 expression do not correlate with apoptosis arrest in our patients. As expected, we noted a negative correlation of p53 with a high apoptotic index ($p = .001$) [7].

Viruses are recognized for their tendency to regulate the host cell apoptotic mechanisms. We suggest that the modulation of apoptosis may be one way in which the MV operates in cHL, perhaps supported by the conservation and stabilization of PIRH2 [7, 43–45].

As we found support in the refutation of the thesis of a cross-reactivity regarding our antibodies, we engaged in new experiments [8, 9]. We carried out a Western blot with frozen tissues from 18 cases of non-small cell lung cancer and with a sample of lung tissue remote from the tumor, using anti-P-MV antibody (9H4): sc-101,356, Santa Cruz Biotechnology, INC, Europe. Table 1 describes positive P-MV expression in the majority of lung cancers examined. It is of note that the non-neoplastic lung tissue associated with the above tumors expressed P-MV as well, except in two cases, in which the normal lung expressed the P-MV antigen, while the tumor did not. Expression of the measles virus antigen remote from the tumor may signify that the lung carrying a putative persistent measles infection may expose the patient to the development of malignancy.

We further used the same anti-P-MV antibody on a tissue microarray carrying 80 samples, 20 each from 4 types of epithelial cancers. Table 2 shows in the bulk of tumors, predominant staining of the nuclei, whereas the cytoplasm stained often weak or negative. Shuttling of measles virus proteins between the infected cell nucleus and its cytoplasm has previously been described [46].

New Aspects of the Research

Atypical measles syndrome (AMS) is a condition which is not only diagnosed infrequently and often missed, but of which many physicians are totally unaware.

This syndrome is related with the inactivated anti-MV vaccines in formalin with the Edmonston B strain of MV. In one of its forms, the FIMV (formalin inactivated measles vaccine), it was given in three separate doses, from 1963 to 1967. Following this form of the vaccine, moderate levels of inhibiting antibodies only emerged, but low levels of complement-fixing antibodies developed. The protection acquired lasted a few months only, while the patients were at risk of showing symptoms and signs of a more severe disease first named atypical measles [47]. Reproduced in macaques, this form of the disease was considered by the scientists [48] to follow a primary infection which raised a non-protective type II CD4 T-cell response but not from the absence of a functional antibody against the fusion protein. Subsequent to a secondary exposure to a wild-type MV, an anamnestic (recall-related) production of a low-avidity antibody may be the cause of immune complexes deposition [49].

The atypical measles syndrome includes a very high temperature, skin lesions [50], pneumonitis which may be long standing [51], abdominal pain, transient hepatitis

Table 2 Expression of the measles virus phosphoprotein in epithelial cancers originating in four different organs, by tissue microarray

Organ	Nucleus pos (%)	Cytoplasm pos (%)	Stroma pos (%)	Inflammation (%)
Lung	10 (52.6)	2 (11.1)	0	1 (5.56)
Colon	13 (68.4)	7 (36.8)	4 (23.5)	2 (11.8)
Stomach	14 (73.7)	4 (21)	0	2 (10.5)
Breast	15 (75)	10 (50)	2 (10)	0

Lung cancers - adenocarcinoma; squamous cell carcinoma

Colon cancers - adenocarcinoma; tubular (+/− papillary)

Stomach cancers - adenocarcinoma; signet ring cell carcinoma; mucinous

Breast cancers - invasive; papillary; scirrhous; non-invasive papillary; lobular

[52], headache, pleural effusions and eosinophilia. These signs and symptoms are usually absent in classical measles, and may occur as long as 16 years after the FIMV vaccination [47]. Atypical measles syndrome is still described today, although officially the FIMV vaccine has been banned since 1967 [53].

Atypical subacute sclerosing panencephalitis (SSPE), a neurodegenerative disease related with MV, is not included in AMS. However, it differs from the classical form of SSPE by occurring in adults, by having a very short latency or showing atypical clinical or biologic features [54–56]. It is of note, that SSPE, is the only form of the measles complex in which a proven persistent MV infection has been determined.

As the diagnosis of AMS is often made at an age older than the typical age for measles, we propose that it may represent a form of the late host response model to a common infectious agent. Since many practitioners ignore the occurrence of AMS [50, 53], even though it is still prevalent to this day [53], we may contribute to its recognition. The range and type of vaccination these patients previously received should be determined. In addition, some measles patients, described in 1987 [57] and in 2007 [58], present several features consistent with AMS. We also propose to follow the patients with confirmed AMS to identify an eventual malignancy, and which childhood infections the patients have developed.

We suggest to set up a research collaboration which would investigate the epidemiologic aspects of the query that we have initiated [1] and which remains an open end. We encourage scientists to use for that purpose our cohort of cHL patients, about half of whom carry MV proteins in their tumor cells. We incite the investigation of cohorts from Israeli studies, in which the patients may have suffered from AMS [57, 58] and who may develop sometimes in the future a MV-related malignancy.

Providing our thesis is sustained and a successful global effort to eradicate measles is accounted for [59], it may take as much as 20 to 25 years to witness a significant lessening of the incidence of cHL and other MV-related malignant tumors. While, if AMS plays a significant role in these cancers, and since it is primarily related with a formalin inactivated anti-MV vaccination mode, the eradication of this subset of malignancies may occur earlier.

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Compliance with Ethical Standards

Conflict of Interest The authors have declared that no competing interest exists.

References

1. Benharroch D, Shemer Avni Y, Myint Y-Y, et al. (2004) Measles virus: evidence of an association with Hodgkin's disease. Brit J Cancer 91:572–579
2. Maggio E, Benharroch D, Gopas J, Dittmer U, Hansmann M-L, Kuppers R (2007) Absence of measles virus genome and transcripts in Hodgkin-reed/Sternberg cells of a cohort of Hodgkin lymphoma patients. Int J Cancer 121:448–453
3. Wilson KS, Freeland JML, Gallagher A, et al. (2007) Measles virus and classical Hodgkin lymphoma: no evidence for a direct association. Int J Cancer 121:442–447
4. Benharroch D, Klinkovich I, Piura B, Shaco-Levy R, Gopas J (2009) Evidence of measles virus antigens and RNA in endometrial cancer. Eur J Obstet Gynecol Reprod Biol 147:206–209
5. Sion-Vardy N, Lasarev I, Delgado B, Gopas J, Benharroch D, Ariad S (2009) Measles virus: evidence for association with lung cancer. Exp Lung Res 35:701–712
6. Ariad S, Milk N, Bolotin A, Gopas J, Sion-Vardy N, Benharoch D (2011) Measles virus antigens in breast cancer. Anticancer Res 31: 913–920
7. Benharroch D, Einav I, Feldman A, Levy A, Ariad S, Gopas J (2010) Apoptosis of Hodgkin-reed-Sternberg cells in classical Hodgkin lymphoma revisited. APMIS 118:339–345
8. Karlin D, Belshaw R (2012) Detecting remote sequence homology in disordered proteins: discovery of conserved motifs in the N-termini of Mononrgavirales phosphoproteins. PLoS One 7:e31719
9. Kruzniar A, van Ham RC, Pongor S, Leunissen JA (2008) The quest for orthologs: finding the corresponding gene across genomes. Trends Genet 24:539–551
10. Thorley-Lawson DA, Gross A (2004) Mechanism of disease: persistence of Epstein–Barr virus and the origin of the associated lymphomas. N Engl J Med 350:1328–1337
11. Peek RM, Crabtree JE (2006) *Helicobacter* infection and gastric neoplasia. J Pathol 208:233–248
12. Tlsty TD, Coussens LM (2006) Tumor stroma and regulation of cancer development. Annu Rev Pathol 1:119–150
13. Benharroch D, Shemer-Avni LA, Myint Y-Y, Ariad S, Rager B, Sacks M, Gopas J (2003) New candidate virus in association with Hodgkin's disease. Leukemia & Lymphoma 44:605–610
14. Knecht H, Berger C, Rothenberg S, Odermatt BF, Brousset P (2001) The role of Epstein–Barr virus in neoplastic transformation. Oncology 60:289–302
15. Niedobitek G, Meru DHJ (2001) Epstein–Barr virus infection and human malignancies. Int J Exp Pathol 82:149–170
16. Jarrett RF, Armstrong AA, Alexander E (1996) Epidemiology of EBV and Hodgkin lymphoma. Ann Oncol 7(suppl):5–10
17. Chang KL, Albujar PF, Chen YY, Johnson RM, Weiss LM (1993) High prevalence of Epstein–Barr virus in reed-Sternberg cells of Hodgkin disease occurring in Peru. Blood 81:496–501
18. Bargou RC, Emmerich F, Krappmann D, et al. (1997) Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. J Clin Invest 100: 2961–2969
19. Schuhmann KM, Pfaller CK, Conzelmann KK (2011) The measles virus V protein binds to p65 (RelA) to suppress NF-KappaB activity. J Virol 85:3162–3171
20. Rodig SJ, Savage KJ, Nguyen V, Pinkus GS, Shipp MA, Aster JC, Kutok JL (2005) TRAF1 expression and c-Rel activation are useful adjuncts in distinguishing classical Hodgkin lymphoma from a subset of morphologically or immunophenotypically similar lymphomas. Am J Surg Pathol 29:196–203
21. Izban KF, Ergin M, Huang Q, et al. (2001) Characterization of NF-kappaB expression in Hodgkin disease. Mod Pathol 14:297–310

22. MacMahon B (1966) Epidemiology of Hodgkin's disease. Cancer Res 26:1189–1201
23. Gutensohn N, Cole P (1981) Childhood social environment and Hodgkin's disease. N Engl J Med 304:135–140
24. Glaser SL (1990) Spacial clustering of Hodgkin's disease in the San Francisco Bay area. Am J Epidemiol 132(1 Suppl):s167–s177
25. Westergaard T, Melbye M, Pedersen JB, Frish M, Olsen JH, Andersen PK (1997) Birth order, sibship size and the risk of Hodgkin's disease in children and young adults: a population based study of 31 million person-years. Int J Cancer 72:977–981
26. Sleckman BG, Mauch PM, Ambinder RF, et al. (1998) Epstein–Barr virus in Hodgkin's disease: correlation of risk factors and disease characteristics with molecular evidence of viral infection. Cancer Epidemiol Biomark Prev 7:1117–1121
27. Glaser SL, Clarke CA, Nugent RA, Stearns CB, Dorfman RF (2002) Social class and risk of Hodgkin's disease in young adult women in 1988-94. Int J Cancer 98:110–117
28. Urayama KY, Jarrett RF, Hjalgrim H, et al. (2012) Genome-wide study of classical Hodgkin lymphoma and Epstein–Barr virus status-defined subgroups. J Natl Cancer Inst 104:240–253
29. Veit BC, Schyldower M, McIntyre S, Simmons D, Lampe RM, Fearnow RG, Stewart J (1991) Serological response to measles vaccination in a highly immunized military dependent adolescent population. J Adolesc Health 12:273–278
30. Desai VK, Kapadia SJ, Kumar P, Nirupam S (2002) Impact assessment of mass measles vaccination. Ind J Pediat 69:1037–1040
31. Dickinson HO, Nyari TA, Parker L (2002) Childhood solid tumors in relation to infections in the community in Cumbria during pregnancy and around the time of birth. Br J Cancer 87:746–750
32. Tyari TA, Dikinson HO, Parker L (2003) Childhood cancer in relation to infections in the community during pregnancy and around the time of birth. Int J Cancer 104:772–777
33. Zygiert Z (1971) Hodgkin's disease: remission after measles. Lancet 1(7699):593
34. Mota HC (1973) Infantile Hodgkin's disease: remission after measles. Br Med J 2:241
35. Zwitter M (1984) Hodgkin's disease: therapeutic role of measles vaccine. Am J Med 77:A49 A52, A64
36. Schattner A (1984) Therapeutic role of measles vaccine in Hodgkin's disease. Lancet 1(8369):171
37. Cozen W, Hamilton AS, Zhao P, et al. (2009) A protective role for early oral exposures in the etiology of young adult Hodgkin lymphoma. Blood 114:4014–4020
38. Stals A, Mathijs E, Baert L, et al. (2012) Molecular detection and genotyping of noroviruses. Food Environ Virol 4:153–167
39. Bar M, Bar D, Lehman B (2009) Selection and validation of candidate housaekeeping genes for studies of human keratinocytes - review and recommendations. J Invest Dermatol 129:535–537
40. Ariad S, Lipshitz I, Benharroch D, Gopas J, Barchana M (2009) A sharp rise in the incidence of Hodgkin's lymphoma in young adults in Israel. Isr Med Assoc J 11:453–455
41. Chen YT, Zheng T, Chou MC, Boyle P, Holford TR (1997) The increase of Hodgkin's disease incidence among young adults. Experience in Connecticut, 1935-1992. Cancer 79:2209–2218
42. Liu S, Semenciw R, Waters C, Wen SW, Mao Y (2000) Time trends and sex patterns in Hodgkin's disease incidence in Canada, 1970-1995. Can J Public Health 91:188–192
43. Chen M, Cortay J-C, Logan IR, Sapountzi V, Robson CN, Gerlier D (2005) Inhibition of ubiqitination and stabilization of human ubiquitin E3 ligase PIRH2 by measles virus phosphoprotein. J Virol 79: 11824–11836
44. Duan W, Gao L, Druhon LJ, Zhu WG, Morrison C, Otterson GA, Villalona-Calero MA (2004) Expression of Pirh2, a newly identified ubiquitin protein ligase in lung cancer. J Natl Cancer Inst 96: 1718–1721
45. Corcoran CA, Huang Y, Sheikh MS (2004) The p53 paddy wagon: COP1, Pirh2 and MDM2 are found resisting apoptosis and growth arrest. Cancer Biol Ther 3:721–725
46. Nihie T, Nagata K, Takeuchi K (2007) The C protein of wild-type measles virus has the ability to shuttle between the nucleus and the cytoplasm. Microbes Infect 9:344–354
47. Griffin DE, Pan CH (2009) Inactivated vaccines. In: Griffin DE, Oldstone MBA (eds) Measles, pathogenesis and control. Springer, Berlin, pp. 194–195
48. Polack FP, Auwaerter PG, Lee SH, et al. (1999) Production of atypical measles in rhesus macaques: evidence for disease mediated by immune complex formation and eosinophils in the presence of fusion-inhibiting antibody. Nat Med 5:629–634
49. Polack FP, Hoffman SJ, Crujeiras G, Griffin DE (2003) A role for nonprotective complement fixing antibodies with low avidity for measles virus in atypical measles. Nat Med 9:1209–1213
50. Hall WJ, Hall CB (1979) Atypical measles in adolescents: evaluation of clinical and pulmonary function. Ann Intern Med 90:882–886
51. Annunziato D, Kaplan MH, Hall WW, Ichinose H, Lin JH, Balsam D, Paladino VS (1982) Atypical measles syndrome: pathologic and serologic findings. Pediatrics 70:203–209
52. Frey HM, Krugman S (1981) Atypical measles syndrome: unusual hepatic, pulmonary and immunologic aspects. Am J Med Sci 281: 51–55
53. Melenotte C, Cassir N, Tessonnier L, Brouqui P (2015) Atypical measles syndrome in adults: still around. BMJ Case Rep Sept 23: 2015. doi:10.1136/bcr-2015-211054
54. Sachan D (2013) Atypical sclerosing panencephalitis with short onset latency. Indian Pediatr 50:969
55. Malik B, Sharma FJ, Bhardwaj AK, Sharma A (2012) Subacute sclerosing panencephalitis despite adequate vaccination. Australas Med J 5:359–361
56. Fabian VA, Lee HY, Keith-Rokosh JL, de Souza JL, Stewart-Wynne E (2010) A 22-year-old Australian woman with atypical subacute sclerosing panencephalitis diagnosed at postmortem. J Clin Neurosci 17:1192–1194
57. Giladi M, Shulman A, Kedem R, Danon YL (1987) Measles in adults: a prospective study of 291 consecutive cases. BMJ 295: 1314
58. Levine H, Zarka S, Ankol OE, Rozhavski V, Davidovitch N, Aboudy Y, Balicer RD (2015) Seroprevalence of measles, mumps and rubella among young adults, after 20 years of universal two-dose MMR vaccination in Israel. HumVaccin Immunother 11: 1400–1405
59. [No authors listed] (2015) Progress toward regional measles elimination, worldwide, 2000–2014. Wkly Epidemiol Rec 90:623–31.