Indian J Med Res 139, June 2014, pp 952-953

Correspondence

Can Parvovirus B19 infection be naturally oncolytic: clinical findings raise such a possibility in leukaemic children

Sir,

Oncogenic viruses are known for long but oncolytic viruses got highlighted recently. Tumour regression after natural measles virus infection/vaccinations has been observed in cases with leukaemia[1]. Currently, virotherapy of cancer using genetically engineered replication competent oncolytic viruses is a new biological weapon for cancers resistant to conventional anticancer therapies[2]. However, there are no reports on whether human parvovirus B19 (B19) has oncolytic property, though B19 is known to be associated with a wide range of clinical manifestations[3].

Among many studies done by our group over the last one and a half decade on the implications of B19 infection in various clinical diseases data there were two studies involving children where mortality data and one year follow up data were available. Mortality patterns were assessed with respect to recent B19 infection based on the presence of anti-B19 IgM antibodies or B19 DNA in the serum.

The first pilot study comprised 35 children with haematological malignancies (newly diagnosed) mostly with ALL (acute lymphoblastic leukaemia) and six children (17.1%, 5 ALL, 1 non-Hodgkin lymphoma, NHL) were found to have B19 infection compared to one in 34 controls ($P < 0.05$)[4]. On comparing death rates among 29 B19 uninfected children, five children with haematological malignancies (17.1%) died in contrast to no deaths among six B19 infected group. The reason for this difference in mortalities remained unknown. A similar observation was found in case of a 13yr old male on treatment for CLL (chronic lymphocytic leukaemia) who was referred to our laboratory for investigation of unexplained prolonged chronic anaemia in March 2007. The child was positive for anti-B19 IgM antibodies by ELISA and B19 DNA by nested-PCR in the serum. Normally there are periods of remission and relapse in leukaemia but this child continued with remission for over one year and did not relapse (our unpublished data).

These findings on mortality (no deaths among B19 infected ALL patients and a case of CLL with prolonged remission) have raised an indication that natural B19 infection may have an unexplored oncolytic effect. Further the mechanism of such oncolysis may be due to apoptosis induced by B19 NS1 proteins[5] or through toll like receptors (TLRs) activating nuclear factor kappa beta (NF-κB) transcription[6]. It may be noted here that though B19 virus primarily infects human erythroid lineage cells but it has also been detected in non-erythroid lineage cells *in vivo*, however, the mechanism of infection is not clear[7,8]. Thus B19 infected malignant blast cells may also be destroyed through apoptotic mechanism defraying deaths for a while[9]. It may also be noted here that the actual number of B19 infected cases could be more than that detected because B19 might remain in cryptic sites and viral titres might be low. Besides, children may fail to produce sufficient quantities of IgM antibodies owing to immune suppression due to malignancy and cytotoxic drugs. In another study[10], B19 infection in children with ALL caused prolonged interruptions of chemotherapy and this may explain prolonged remission in the present case with CLL.

Our observations got further support after literature survey[5-7,11-15] which revealed that rodent autonomous parvovirus H-1(H-1PV) that is non-pathogenic for human has strong intrinsic oncotropism, oncolytic activity and natural oncosuppressive effects against human tumours[5]. The first oncolytic preparation of H-1PV (ParvOryx) is undergoing phase I/IIa clinical trial in patients with primary or recurrent glioblastomamultiforme[11]. Recently it has been reported that H-1PV besides having an intrinsic oncolytic

activity is able to enhance NK (natural killer) cell-mediated killing of tumour cells and can act as adjuvant and stimulate anti-tumour immune responses[12,13]. More recently, H-1PV has been tried as a potential therapy against cervical and pancreatic carcinomas[14]. Besides naturally oncolytic measles virus[15] several other oncolytic viruses like reovirus, herpes and vaccinia virus are in the late phase of clinical trials and may be combined with radio-or chemotherapy[16].

These corroborative findings reported in literature further support our preliminary view that B19 virus may possibly be naturally oncolytic in leukemic children but because of a very small sample size and poor statistical significance these observations need to be interpreted with caution. Further investigations are warranted with large samples to verify this observation and to unveil a new dimension in the virotherapy of haematological malignancies specially ALL.

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References

1. Pasquinucci G. Possible effect of measles on leukaemia. *Lancet* 1971; *1* : 136.
2. Parrula C, Fernandez SA, Zimmerman B, Lairmore M, Niewiesk S. Measles virotherapy in a mouse model of adult T-cell leukaemia/lymphoma. *J Gen Virol* 2011; *92* : 1458-66.
3. Kishore J, Kapoor A. Erythrovirus B19 infection in humans. *Indian J Med Res* 2000; *112* : 149-64.
4. Kishore J, Sen M, Kumar A, Kumar A. A pilot study on parvovirus B19 infection in paediatric haematological malignancies. *Indian J Med Res* 2011; *133* : 407-13.
5. Nüesch JP, Lacroix J, Marchini A, Rommelaere J. Molecular pathways: rodent parvoviruses--mechanisms of oncolysis and prospects for clinical cancer treatment. *Clin Cancer Res* 2012; *18* : 3516-23.
6. Sieben M, Schäfer P, Dinsart C, Galle PR, Moehler M. Activation of the human immune system via toll-like receptors by the oncolytic parvovirus H-1. *Int J Cancer* 2013; *132* : 2548-56.
7. Munakata Y, Kato I, Saito T, Kodera T, Ishii KK, Sasaki T. Human parvovirus B19 infection of monocytic cell line U937 and antibody-dependent enhancement. *Virology* 2006; *345* : 251-7.
8. Munakata Y, Saito-Ito T, Kumura-Ishii K, Huang J, Kodera T, Ishii T *et al*. Ku80 autoantigen as a cellular coreceptor for human parvovirus B19 infection. *Blood* 2005; *106* : 3449-56.
9. Singh PK, Doley J, Kumar GR, Sahoo AP, Tiwari AK. Oncolytic viruses & their specific targeting to tumour cells. *Indian J Med Res* 2012; *136* : 571-84.
10. Lindblom A, Heyman M, Gustafsson I, Norbeck O, Kaldensjö T, Vernby A *et al*. Parvovirus B19 infection in children with acute lymphoblastic leukemia is associated with cytopenia resulting in prolonged interruptions of chemotherapy. *Clin Infect Dis* 2008; *46* : 528-36.
11. Geletneky K, Huesing J, Rommelaere J, Schlehofer JR, Leuchs B, Dahm M, *et al*. Phase I/ IIa study of intratumoral/ intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastomamultiforme: ParvOryx01 protocol. *BMC Cancer* 2012; *12* : 99.
12. Bhat R, Dempe S, Dinsart C, Rommelaere J. Enhancement of NK cell antitumor responses using an oncolytic parvovirus. *Int J Cancer* 2011; *128* : 908-19.
13. Grekova SP, Rommelaere J, Raykov Z. Parvoviruses-tools to fine-tune anticancer immune responses. *Oncoimmunology* 2012; *1* : 1417-9.
14. Li J, Bonifati S, Hristov G, Marttila T, Valmary-Degano S, Stanzel S, *et al*. Synergistic combination of valproic acid and oncolytic parvovirus H-1PV as a potential therapy against cervical and pancreatic carcinomas. *EMBO Mol Med* 2013; *5* : 1537-55.
15. Boisgerault N, Guillerme JB, Pouliquen D, Mesel-Lemoine M, Achard C, Combredet C, *et al*. Natural oncolytic activity of live-attenuated measles virus against human lung and colorectal adenocarcinomas. *Biomed Res Int* 2013; *2013* : 387362.
16. 15. Alemany R. Viruses in cancer treatment. *Clin Transl Oncol* 2013; *15* : 182-8.