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Increased IL-6 detection in adult and pediatric lymphoid tissue harboring Parvovirus B19

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ABSTRACT

Background: Parvovirus B19 (B19V) is a common pathogenic virus infecting humans. Previous studies have shown evidence of B19V infection in patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma using ELISA and PCR on serum specimens. B19V nonstructural protein is known to alter the expression of cellular factors including interleukin-6 (IL-6), which can increase the risk for and worsen the prognosis of lymphomas.
Objective: The objective of this study was to detect B19V capsid protein and IL-6 expression in normal and malignant lymphoid tissue, as well as any correlation between the two.
Study design: IHCs for B19V capsid protein, IL-6, and B19V co-receptors P-antigen and α5β1 integrin were performed on a tissue array containing 70 duplicated pediatric and adult lymphoma tissues and 5 duplicated benign lymph node sections. Cases were identified as normal, B-cell NHL, diffuse large B-cell NHL, Hodgkin's lymphoma, extranodal NK/T cell lymphoma, anaplastic large cell lymphoma, or mantle cell lymphoma. IL-6 and B19V capsid staining were quantified using a positive pixel count algorithm, and P-antigen and α5β1 staining using a membrane quantification algorithm.
Results: B19V capsid protein was detected in both benign and malignant lymphoid tissue. The Spearman rank correlation coefficient analysis was performed to determine the relationship between the level of positivity for B19V and IL-6 staining, yielding an overall correlation coefficient of 0.679 (p-value < 0.0001).
Conclusions: Our results show a moderate correlation between the levels of positive B19V and IL-6 staining by IHC, indicating a possible role for B19V in the pathogenesis of lymphomas.

1. Background

Parvovirus B19 (B19V) is a common human pathogenic virus. Its single-stranded DNA genome encodes three major nonstructural proteins and two capsid proteins, VP1 and VP2. Well-documented diseases caused by B19V include erythema infectiosum (fifth disease) in children, arthropathy in adults, transient aplastic crisis in individuals with shortened red blood cell survival, and chronic anemia in immunocompromised hosts.[1] The spectrum of B19V-induced diseases has been broadening, with numerous studies implicating B19V as a causative agent for thrombocytopenia, myocarditis, hepatitis, a range of autoimmune diseases and various neurological disorders.[2–6]

Viral persistence has been described not only in immunocompromised individuals, but also in symptomatic and non-symptomatic immunocompetent individuals.[7,8] B19V is only known to replicate in erythroid progenitor cells that contain the main cellular receptor for B19V infection, blood group P-antigen,[9] as well as two identified co-receptors, α5β1-integrin[10] and Ku80.[11] Yet after apparent clearance of infection, B19V DNA has been detected in serum samples and may persist in various tissues

Abbreviations: Parvovirus B19, (B19); Nonstructural protein, (NS1); Capsid proteins, (VP1 and VP2); VP unique region, (VPu); Interleukin-6, (IL-6); Immunohistochemistry, (IHC); Non-Hodgkin's lymphoma, (NHL); Tumor necrosis factor, (TNF-α).

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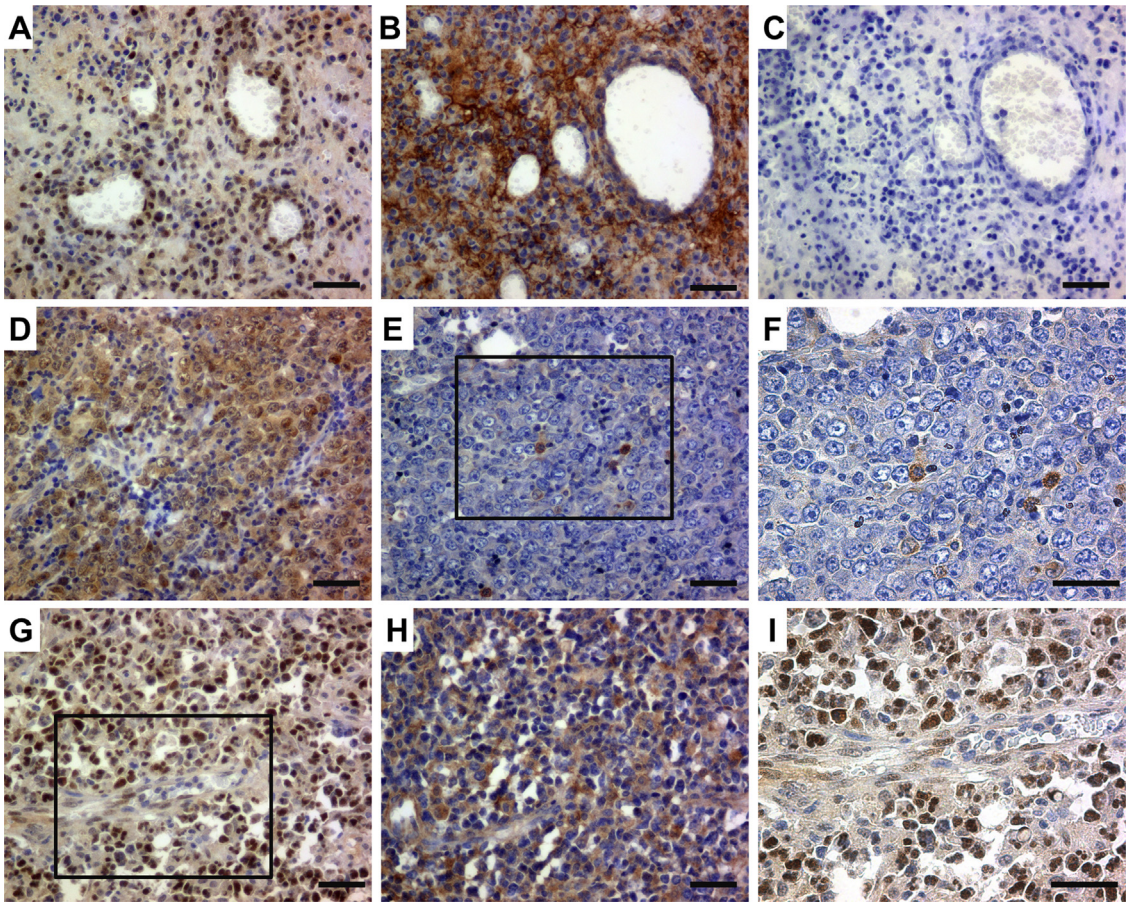

Fig. 1. Patterns of B19V staining and IL-6 production. Row 1 (A–C) is an anaplastic large cell lymphoma section taken from the right inguinal lymph node of a 69-year-old man. Row 2 (D–F) is a NHL, B-cell type taken from the pharyngeal region of an 81-year-old female. Row 3 (G–I) is a NHL, B-cell type taken from the stomach of a 51-year-old male. Column 1 (A–G) represents the stain for B19V capsid protein and column 2 (B–H) the stain for IL-6. (A) Mostly positive nuclear staining for B19V VP1/VP2 in the lymphocytes, but also in the endothelial cells; there is very strong corresponding IL-6 production (B). (C) IgG control for tissues seen in (A). (D) B19V staining is much more cytoplasmic, and localized to the larger neoplastic lymphocytes with the smaller lymphocytes staining negatively, but the corresponding IL-6 staining (E) is relatively low, with IL-6 being produced mostly by the non-neoplastic infiltrating cells, most likely plasma cells (F). Figure (G) shows strong nuclear B19V staining of the neoplastic lymphocytes, macrophages, and also endothelial cells (enlarged in (I)), with strong corresponding production of IL-6 (H). Scale bars represent 25 μm.

including skin, myocardial endothelium, tonsils, liver, thyroid, testis, brain, synovia.[12–16]

Lymphomas are tumors composed of neoplastic lymphocytes or very rarely histiocytes. They are broadly classified into Hodgkin's and non-Hodgkin's (NHL) types, the former distinguished from the latter by the presence of the neoplastic Reed–Sternberg giant cell. The median age at diagnosis for Hodgkin's lymphoma is 38 years, compared to NHL at 66 years.[17] Greater than 85% of NHLs are derived from B-cells, ~12% from T-cells, and a very small number from histiocytes.[18]

In a previous study, evidence of B19V infection was detected in 5/10 (50%) subjects with NHL and 3/8 (37.5%) subjects with Hodgkin's lymphoma using ELISA and PCR on serum specimens.[19] In some cases, the oncogenic functions of lymphomas may depend on the expression of viral genes, as is the case with EBV-induced lymphomas where the viral genes expressed differ among tumor types.[20] Full replication would not be necessary for B19V to influence lymphoma development. B19V NS1 is known to alter the expression of cellular factors including interleukin-6 (IL-6),[21] which is known to increase the risk for and worsen the prognosis of lymphomas.

In this report, we demonstrate B19V infection of the immune cells of adult and pediatric lymphomas as well as in benign lymph node sections, and show a correlation between levels of B19V and IL-6 positivity. To determine the susceptibility of cells in different disease states to infection with B19V, all samples were also tested for the presence of P-antigen and α5β1.

2. Objective

The objective of this study was to detect B19V capsid protein and IL-6 expression in normal and malignant lymphoid tissue, as well as any correlation between the two.

3. Study design

3.1. Samples

Seventy-five duplicated sections of 0.5 μm thick formalin-fixed, paraffin-embedded (FFPE) tissues of various types of lymphoma and benign lymphoid tissues were examined (Biochain, Z7020070). Subject ages ranged from 7 to 84 years old, with a mean age of 50.3 years and standard deviation of 18.8 years. Cases were identified by Biochain as being either B-cell NHL ($n = 45$), diffuse large B-cell NHL ($n = 6$), Hodgkin's lymphoma ($n = 11$), extranodal NK/T cell lymphoma ($n = 3$), anaplastic large cell lymphoma ($n = 4$), mantle cell lymphoma ($n = 1$), or benign lymph nodes ($n = 5$). This study followed the World Medical Association's Declaration of Helsinki.