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Review

Viral diseases affecting the pleura

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ABSTRACT

Background: Viruses affect the human body in multiple ways producing various disease states. The infections of the pulmonary parenchyma have been well described. However, there has been no current review of the literature pertaining to the pleura.
Aim: To review the available literature pertaining to diseases of the pleura that are caused by viral infections.
Methods: A Medline search was performed and available research and review articles relating to viral infections that resulted in pleural effusions, pleural masses, pleural thickening, and pleural nodularity were reviewed.
Conclusion: There are numerous viruses that cause diseases of the pleura. Pleural effusions and lesions within the pleura are the most common presentation of the disease state. Polymerase chain reaction has the potential to further diagnose viral infections and expand our knowledge base in this field.

Contents

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1. Introduction

The pulmonary parenchymal manifestations of viral infection have been well characterized. However, to date, there has not been an effort to review the current body of literature of their effects on the pleura. For over 100 years, investigators have discovered, with increasing frequency, viruses that cause a myriad of maladies ranging from meningo-encephalitis to malignancies, such as hepatocellular carcinoma from Hepatitis B Virus and cervical cancer from the human papilloma virus. Viruses are responsible for some of the largest pandemics in recent history. Arguably, one of the single greatest advances of our time was the development of vaccines targeted against these viruses, thereby, lengthening the lifespan of humans significantly.

According to Cohen and Sahn, the incidence of pleural effusions in viral pneumonia has been reported to be 2–9% [1]. However, when examined by radiology, in the lateral decubitus position, 18% of viral pneumonias develop an effusion [1]. Influenza viruses, parainfluenza viruses, respiratory syncytial virus, herpes simplex virus, cytomegalovirus, measles virus, varicella zoster virus (VZV), and adenovirus have been reported to cause pleural effusions, particularly in immunocompromised patients. In general, these effusions are small and typically resolve within two weeks [1,2]. Hantavirus has also been commonly associated with pleural effusions and may be the result of pulmonary capillary leak or possibly renal failure [2].

Viral infection has been postulated as one of the most common causes of inflammation of the pleura [3]. In this review, we describe the most common viruses that have been reported including influenza, coxsackievirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), adenovirus, human herpesvirus-8 (HHV-8), dengue, human t-lymphotropic virus type 1 (HTLV-1), simian virus 40 (SV40), parvovirus B19, varicella, herpes simplex virus (HSV), and epstein–barr virus (EBV).

2. EBV/HHV-8

Pyothorax-associated lymphoma (PAL) is a non-Hodgkin lymphoma arising from B-cells occurring in individuals who were treated for tuberculosis (TB) with pneumothorax years prior. The cellular histology of PAL is diffuse large B-cell lymphoma; however, there has been a reported association with infection with EBV and the expression of the latent genes EBNA-2, LMP-1 and EBNA-1 [4]. HHV-8 genomes have been found consistently in primary effusion lymphoma (PEL) characterized by malignant effusions and immunoglobulin gene rearrangements [5].

PEL has been associated with HHV-8 infection that has been documented in pleural effusions in patients who are HIV negative [6]. In contrast, it appears that patients with PAL typically have EBV that hypothetically results in immortalization of B-lymphocytes, as shown in vitro, and that the thick hyalinous and acellular matrix of a fibrothorax is a particular niche for EBV-infected B-cells [7–9]. Typically, these lymphomas are of large B-cell type but immunoblastic lymphoma has also been reported [7–19]. Other studies have shown documented HHV-8, without EBV, associated with PAL [20]. Another hypothesis for a tropism for serosal cavities is due to increased vascular endothelial growth factor (VEGF) and vascular permeability factor (VPF) in conjunction with decreased adhesion receptor intracellular adhesion molecule (ICAM-1) [20]. HIV patients have been documented to have a high-grade B-cell phenotype of non-Hodgkins Lymphoma that are both EBV and HHV-8 positive [21]. Further case studies of PAL have confirmed the presence of EBV but also introduced the possibility of co-infection with HHV-8 in the setting of a diffuse large B-cell morphology [17]. One case report of two HIV-negative individuals documented the absence of EBV and presence of HHV-8 DNA in the setting of PEL suggesting that host immnocompetence, older age, and a less aggressive course are characteristic of these patients [19]. Another postulated etiology for the development of PAL would be a subclinical systemic and/or local immunodeficiency that occurs in chronic tuberculosis patients which may favor lymphoma development [22].

When examining patients with known HIV and KS, a rate as high as 30% has been quoted as to the involvement of the pleural and pulmonary parenchyma [23]. HHV-8 related diseases have a morphology of numerous atypical mesothelial cells in a polymorphous lymphoid background [23]. Direct infection with HHV-8 may initiate serositis and cytokine production and induce proliferation of PEL cells [23]. Tumor morphologies that have been described in AIDS patients with PEL by Cesarman and others [24] include large-cell immunoblastic lymphoma and anaplastic large-cell lymphoma. They found co-infection with EBV and HHV-8 in 86% of the cases in agreement with the findings of Engels et al. [24,25].

However, other studies suggest that EBV located within the pleural space indicates local reactivation of the virus [26]. This is corroborated by a case report in 1996 that found reactivation of latent EBV in a bone marrow transplant patient as the most probable cause of his B-cell lymphoproliferative disease [27]. Interestingly adenovirus type 2 pneumonia and infection of the lymphoma infiltrating the lung but not in adjacent lymphoma within the lung, stomach, and duodenum indicating that this infection occurred after the neoplastic process began [27]. Other co-factors likely play a role in the development of lymphoma through local immunosuppression. Regulatory cytokines such as IL-10 and transforming growth factor (TGF)-β1 exertion immunosuppression by suppressing antigen-specific CTL induction and cytokine production of macrophages and helper T cells [28]. They also observed that IL-2 & interferon-γ, immunopotentiating cytokines, were not excreted from the lymphoma cell lines, and yet another explanation may be the immunosuppressive effects of imglammatory cells locally [28]. That being said, there is still some suggestion that monitoring viral load may be useful in monitoring the response of PAL to treatment [29].

3. Dengue virus

Dengue is a disease characterized by infection with dengue virus, fever, headache, eye pain, myalgias, arthralgias, and rash. Dengue hemorrhagic fever (DHF) is distinct in that it presents with defects in hemostasis and plasma leakage. There are approximately 100 million cases of Dengue Fever (DF) annually and over 250,000 cases of DHF annually. In a study published in 2000, Vaughn and others examined 168 children in Thailand enrolled prospectively at two hospitals. Eighty-eight patients had Dengue Fever and eighty had DHF. Only 2% of the patients with dengue fever had a pleural effusion compared to 90% of the patients with grade 1 and 2 DHF and 92% of patients with grade 3 DHF. The fluid was not sampled, but it does raise the question of whether the plasma leakage is a direct cause of the pleural effusion, given the markedly increased frequency with DHF [30]. These results mirror the results of others investigating the use of ultrasound in DF and DHF [31–34].

4. Coxsackie B5 virus

Coxsackie B viruses have been described in association with epidemics of pleurodynia since 1949. In 1958 in Ontario, Canada, four children who presented with acute pericarditis and nine with pleurodynia with Coxsackie B5 virus isolated from the feces. They characterized pleurodynia as a severe, sharp pain in the anterior or posterior chest, aggravated by deep inspiration or cough. On

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