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【 CASE REPORT 】

Hepatitis B Virus-associated Vasculitis: Multiple Cavitary Masses in the Lung Mimicking Granulomatous Polyangiitis

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Abstract:
Hepatitis B virus (HBV) is one of the main causes of polyarteritis nodosa (PAN). We herein report a rare case of HBV-associated vasculitis presenting with multiple pulmonary nodules, mimicking granulomatous polyangiitis (GPA), with no abnormalities of the ear, nose, or kidney. A surgical lung biopsy revealed geographic necrosis surrounded by palisading granuloma and capillaritis. Because the HBV surface antigen was positive with a serum HBV-DNA level of 2.9 log10 copies/mL, we first treated the patient with entecavir and 2 weeks of prednisone 50 mg/day. The pulmonary nodules resolved, and seroconversion was observed after one month.

Key words: hepatitis B virus-associated vasculitis, granulomatous polyangiitis, seroconversion, entecavir, short-term corticosteroid

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Introduction

Hepatitis B virus (HBV)-associated vasculitis is a vasculitis associated with probable etiology, and most cases develop HBV-polyarteritis nodosa (PAN), according to the 2012 revised international Chapel Hill consensus conference nomenclature of vasculitis (1). In general, HBV-PAN shows very similar symptoms to those of non-HBV-PAN. PAN is a necrotizing arteritis of the medium and small arteries, typically accompanied by a fever, malaise, weight loss, arthralgia, peripheral neuropathy, palpable purpura, and gastrointestinal bleeding. However, PAN is not associated with antineutrophil cytoplasmic antibodies (ANCA), and the lungs are usually spared (2). While a few reports of various clinical presentations of HBV-PAN have been published (3-6), there are no reports of HBV-associated vasculitis presenting with granulomatous polyangiitis (GPA)-like granulomatous lung nodules.

With respect to the treatment of HBV-PAN, plasma exchange (PE), antiviral drugs, and short-term corticosteroids were proposed in a French study, with the aim of clearing immune complexes, suppressing HBV replication, and controlling the ongoing inflammatory process (2). In one large prospective observational study conducted by the French Vasculitis Study Group, seroconversion was a promising factor for no future relapse (7). However, precisely how to induce seroconversion remains unclear, as no randomized controlled studies have been conducted, due to the condition's rarity.

We herein report a rare case of HBV-associated vasculitis presenting with multiple cavitary nodules of necrosis, palisading granuloma, and capillaritis mimicking GPA in the lung. Seroconversion was successfully induced, and the lung nodules all resolved with entecavir and two weeks of short-term prednisone.

Case Report

A 44-year-old woman presented to our clinic with a chief complaint of a few months' history of hemoptysis, cough, general fatigue, and weight loss. Her family doctor diagnosed her with pneumonia and prescribed clarithromycin and sultamicillin tosylate sequentially. She took these medications for about a month; however, her symptoms did not resolve. The doctor then referred her to our clinic with a

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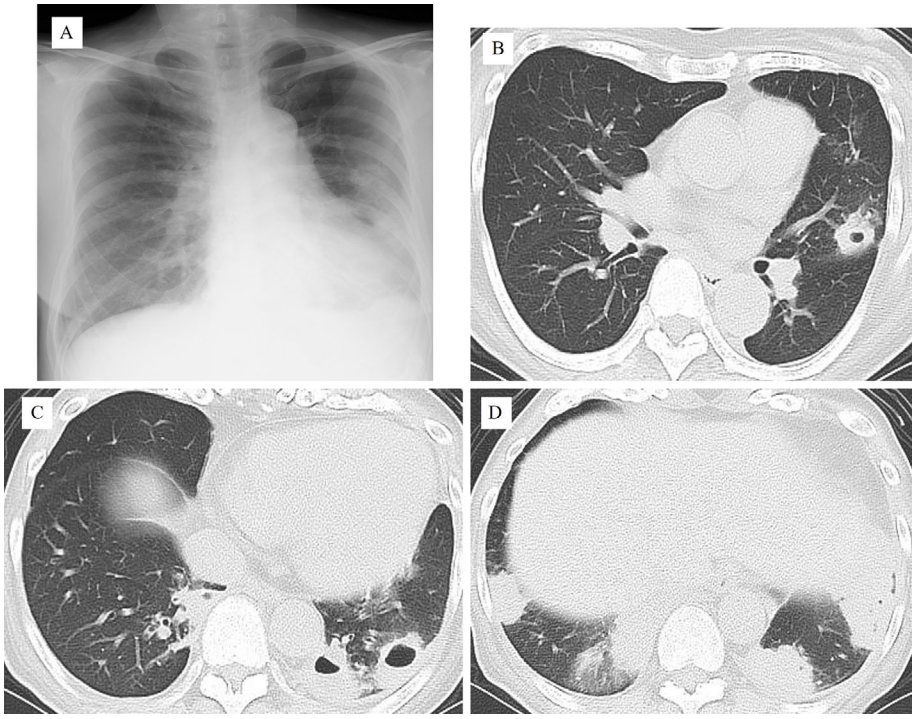

Figure 1. Imaging findings at the initial examination. A: Chest radiograph showing bilateral consolidation of the mediastinal side of the lower lung fields. B, C, D: High-resolution CT revealing multiple cavitary nodules in both lower lobes.

suspicion of pulmonary tuberculosis.

Her medical history was notable for subarachnoid hemorrhaging of unknown etiology nine years earlier. She was a non-smoker who worked in a variety retail store, and her dust and bird exposure were unremarkable. According to her family history, her sister was an HBV carrier from mother-to-child transmission. The patient showed no abnormal vital signs or findings on a physical examination, including lung auscultation, skin, and musculoskeletal assessments. The modified Medical Research Council scale was 0. Laboratory examinations showed leukocytosis (white blood cells 18,400/μL with 90% neutrophils), thrombocythemia (570,000/μL), normal liver and renal functions, and high C-reactive proteinemia (6.19 mg/dL). Autoimmune antibody tests were negative for the following: anti-nuclear antibody, rheumatoid factor (8.0 IU/mL), anti-cyclic citrullinated peptide (CCP) antibody (3.4 U/mL), PR3-ANCA (1.0> U/mL), and myeloperoxidase (MPO)-ANCA (13.1 U/mL). C4, C1q, and CH50 were within normal limits. HBV surface antigen was positive (5,268 IU/mL); however, HB surface antibody and envelope antigen/antibody were negative. The HB-DNA level was 2.9 log10 copies/mL, and the HBV was type C. Urine was negative for blood, casts, and protein.

Chest X-ray revealed bilateral increased density in the lower lung fields (Fig. 1A). Chest computed tomography (CT) revealed bilateral multiple cavitary nodule-like consolidations, predominantly in peripheral sites in the lower lobes (Fig. 1B). Acid-fast staining of her sputum was tested for three consecutive days, with negative findings shown.

We therefore started amoxicillin and clavulanate potassium for a week; however, the imaging studies did not change at all, and the sputum culture grew normal flora. Given the history of non-resolving pneumonia with antibiotics, we hospitalized her for further testing. On admission day 3, a transbronchial cryobiopsy of one of the nodules in the right lower lobe revealed an abscess, organizing pneumonia, and marked hemosiderin deposition, suggesting infection or vasculitis associated with hemorrhaging; nevertheless, the biopsy was not diagnostic (Fig. 2A). No microorganisms were detected on lung tissue culture. On admission day 12, a surgical lung biopsy was performed (Fig. 2B-D), and the specimen revealed geographic necrosis surrounded by palisading granuloma and multinucleated giant cells. Surrounding lung parenchyma showed capillaritis infiltrated with neutrophils, and no microorganisms were identified with Ziehl-Neelsen and Grocott stains. Therefore, histological GPA was suspected. However, there were no abnormal findings in her ears or nose as observed by an otolaryngologist, nor were any kidney abnormalities noted.

In a multidisciplinary discussion, we decided on a diagnostic/therapeutic plan according to the classification algorithm of vasculitis proposed by Watts et al. (8) for lung-limited granulomatous polyangiitis after treating HBV-associated vasculitis. Entecavir treatment was started from admission day 34 (Fig. 3A). After a week of treatment with entecavir, her symptoms of hemoptysis worsened, and follow-up CT showed that all multiple cavitary nodules had enlarged (Fig. 3B). We started 50 mg/day (1 mg/kg) oral prednisone for only 2 weeks in addition to entecavir, and her symptoms rapidly ameliorated. The lung nodules also

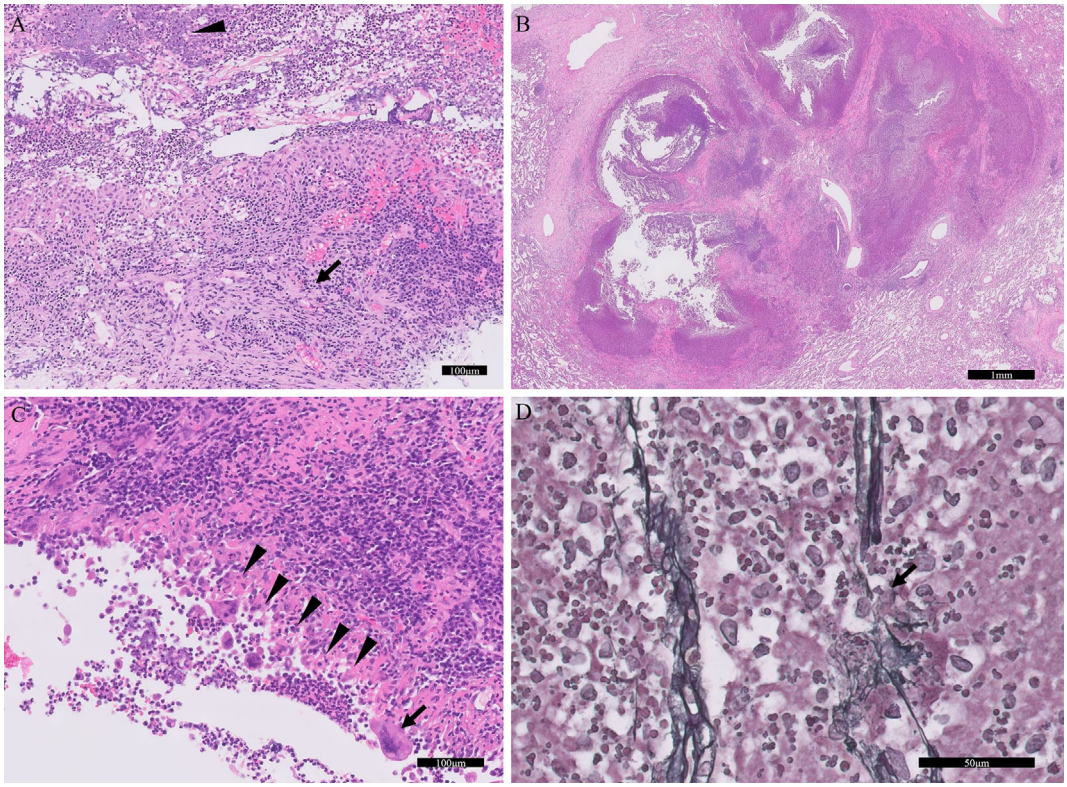

Figure 2. **Histopathologic findings of the surgical lung biopsy (black bars show magnification scale). Cryobiopsy specimen showing abscess (arrowhead) and organizing pneumonia (arrow) [A: Hematoxylin and Eosin (H&E) staining]. Surgical lung biopsy specimen showing geographic necrosis (B: H&E staining), palisading granuloma (arrowheads) and giant cells (arrow) (C: H&E staining), and disruption of the capillary wall (arrow) with neutrophilic infiltration (D: silver impregnation stain).**

dramatically resolved on admission day 59 (Fig. 3C), and she was finally discharged.

At the outpatient clinic one month after admission, all lung nodules had disappeared, and seroconversion had been successfully attained as follows: HB surface antigen decreased to 1,173 IU/mL, HBV envelope antibody became positive (99 IU/mL), and HBV-DNA level was undetectable.

Discussion

The classification of vasculitis has been an area of controversy; there remain some probable etiologies, including HBV (1). In this case, the differential diagnosis of PAN and GPA was important. Given the classification of the American College of Rheumatology (9, 10), only weight loss and HBV corresponded to PAN, whereas the radiological and pathological domains were both satisfied by GPA. However, because lung-limited GPA is very rare (11, 12), and because Watt's algorithm recommends ruling out malignancies, infections (including HBV), drugs, and other autoimmune diseases first (8), it was important to start treatment for HBV infection prior to treatment for GPA. Fortunately, in the current case, no recurrence or any other findings associated with systemic vasculitis have been observed, and the MPO-ANCA level remained at low titers (10 to 20 U/mL).

Although the presence of serum ANCA has proven useful for the diagnosis of ANCA-associated vasculitis in appropriate clinical setting, it is often elevated in a non-specific manner (13). In previous studies for hepatitis virus infection, the frequency of ANCA was not low in patients with HBV and hepatitis C virus (HCV) infection, and some patients with hepatitis virus infection demonstrated ANCA-associated vasculitis (3, 14, 15). The pathogenesis of hepatitis virus triggering autoantibodies or autoimmune disease, such as ANCA or ANCA-associated vasculitis, remains unknown. While it is true that there is no way to prove the extent of HBV in lung tissue, the diagnosis of the current case with HBV-associated vasculitis is considered to be an important finding for such patients.

According to the literature on HBV-associated vasculitis, HBV-PAN is the major presentation, and the lung is usually spared (1, 7). There are various case reports of other exceptional presentations, including cryoglobulinemic vasculitis, ANCA-associated vasculitis, and alveolar hemorrhaging (3-5, 16). This might suggest heterogeneity in HBV-associated vasculitis. Naniwa et al. reported one case presenting with multiple lung nodules, similar to the current case, although without granulomatous changes. That case turned out to be HBV-PAN (17). The current case demonstrated pathological rarity in light of its lung-limited GPA-

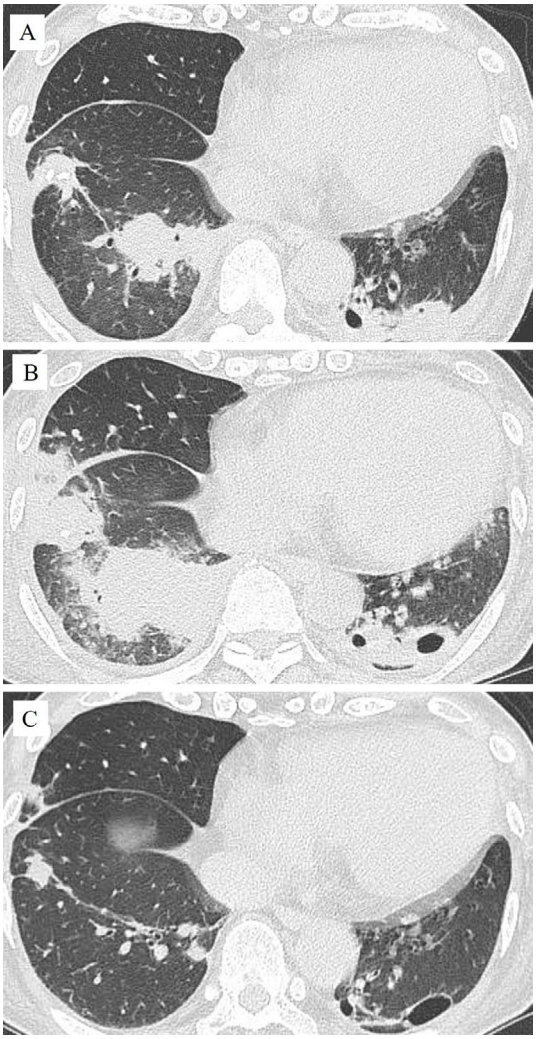

Figure 3. High-resolution CT findings at day 34 (A), 40 (B), and 59 (C). A: The bilateral nodules in the lower lobes were stable compared with the initial evaluation. B: The nodules had all grown, and there were increased numbers of cavitary lesions. C: The nodules were dramatically resolved.

like inflammation due to HBV infection, contributing to the diversity among reports of HBV-associated vasculitis.

Considering the risk of HBV reactivation with corticosteroid treatment, we decided to treat her with entecavir first. However, both her hemoptysis and lung nodules worsened dramatically in the week following entecavir administration. In terms of the pathogenesis of HBV-associated vasculitis, this was assumed to be a type III or immune complex reaction with HB surface antibody affecting the vascular wall (2). Colonno et al. reported transient increases in HB surface antigen levels within the initial eight weeks from entecavir treatment in a woodchuck model (18); therefore, the initial exacerbation in the current case might have been due to immune complex reaction, although this cannot be proven.

The efficacy of oral prednisone in the initial two weeks to control ongoing organ or life-threatening inflammatory processes was reported in several French studies (7, 19). Indeed, the lung nodules in the current case immediately resolved after two weeks of oral prednisone. According to these French studies, seroconversion of HBV was a key prognostic factor for deterring the relapse of HBV-associated vasculitis. Short-term oral prednisone with abrupt stoppage might enhance the immunological clearance of HBV-infected hepatocytes and induce seroconversion from HB surface antigen to HB envelope antibody (7, 19). In a Japanese randomized controlled trial of 42 patients, short-term corticosteroid and abrupt discontinuation were evident for seroconversion in general HBV inflammation (20-22). In the current case, combination therapy with entecavir and short-term prednisone and abrupt discontinuation was appropriate for suppressing HBV replication to control the ongoing inflammation and induce seroconversion.

In conclusion, the current case report describes a rare form of HBV-associated vasculitis presenting with multiple cavitary nodules of necrosis, granuloma, and capillaritis, mimicking GPA in the lung. Corticosteroid treatment led to the resolution of signs and symptoms as well as successful seroconversion.

The authors state that they have no Conflict of Interest (COI).

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