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End-Stage Renal Disease, Autoimmune Hepatitis, Alveolar Hemorrhage and ANCA Vasculitis as a Complication of Chronic Hepatitis B Virus: An Unusual Case Report

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Abstract: Background: End stage renal disease, autoimmune hepatitis and alveolar hemorrhage have rarely been reported as the complications of hepatitis B virus infection that can potentially be triggered by an antibody-mediated vasculitis as a result of a viral infection. The following was a case report detailing a patient presenting with all three of the above presentations who was cytoplasmic antineutrophil cytoplasmic antibody-positive and a chronic carrier of hepatitis B virus. Case presentation: A 52-year-old Malagasy woman presented in our intensive care unit for acute respiratory failure with end-stage renal disease and deterioration in general condition. She was managed with steroids, non-invasive ventilation, and hemodialysis. Laboratory test showed elevated levels of serum creatinine and liver enzymes. An extensive workup was done to find the etiology of elevated liver enzymes. Only blood work that came back positive was for chronic inactive hepatitis virus B and positive autoantibody suggestive of autoimmune hepatitis. A computed tomography scan of her lung revealed features suggestive of bilateral alveolar hemorrhage. Workup for other causes of vasculitis, including anti-neutrophil cytoplasmic antibodies (ANCA) was positive for c-ANCA antibody to proteinase 3. Medical investigations allowed excluding other infectious diseases, malignancies and other rheumatic and vasculitis affections. Administration of lamivudine® orally was done. The patient was followed for more than one year and there were no other new systematic symptoms. Conclusion: This case report showed the possibility of hepatitis B virus-induced vasculitis as the cause of alveolar hemorrhage, autoimmune hepatitis, and end stage renal disease. The origin of these symptoms was attributed to immune complex-mediated vasculitis induced by antineutrophil cytoplasmic antibody.

Keywords: End-Stage Renal Disease, Acute Respiratory Failure, Antineutrophil Cytoplasmic Antibody, Hepatitis B Virus

1. Introduction

Hepatitis B virus (HB) is an established cause of chronic liver disease and hepatocellular carcinoma [1]. It is associated with several extrahepatic manifestations including but not limited to serum sickness, polyarteritis nodosa,

urticaria, leukocytoclastic vasculitis, and essential mixed cryoglobulinemia. In addition to these manifestations, HBV has also been documented to be involved in the etiopathogenesis of antineutrophil cytoplasmic antibodies (ANCA)-positive vasculitis [2]. HBV does not necessarily affect the liver system only but can cause life threatening systemic conditions. A causal relationship has only been firmly established in a few instances of vasculitis, such as chronic HBV infection and polyarteritis nodosa in the literature [3]. While a few reports of various clinical presentations of HBV have been published. There are no reports of the chronic HBV-associated vasculitis presenting with end-stage renal disease, autoimmune hepatitis and alveolar hemorrhage.

Autoimmune hepatitis (AIH) is a serious inflammatory liver disease that results in the autoimmune-mediated destruction of the liver parenchyma, chronic inflammation and fibrosis. Several case studies have associated pathogen infection with the development of AIH. However, a causal relationship between pathogen infection and AIH has yet to be proved [4].

Furthermore, alveolar hemorrhage is severe and potentially fatal medical condition requiring careful attention. Alveolar hemorrhage is vasculitis due to capillaritis. Pulmonary capillaritis may be primary as in ANCA-associated vasculitis or secondary to infections, connective tissue diseases especially systemic lupus erythematosus, or other small vessel vasculitides [5]. HBV has also been widely recognized to be associated with a wide variety of glomerulonephritis, notably membranous nephropathy [6]. Other causes include immunological disorders, inherited diseases, metabolic diseases, and deposition disorder [7].

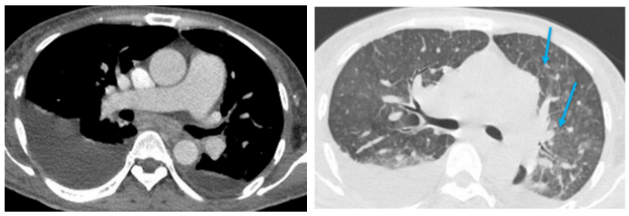
In this paper, we herein report a rare case of HBV-associated vasculitis presenting with end-stage renal disease, with autoimmune hepatitis and alveolar hemorrhage in a patient presenting a cytoplasmic antineutrophil cytoplasmic antibody (ANCA) vasculitis induced by chronic hepatitis B virus.

2. Observation

We reported a 52-year-old Malagasy woman, who was referred to the Internal medicine unit for further evaluation of the end-stage renal disease requiring hemodialysis, associated with transudative pleural effusion and with deterioration in general condition. She also presented hemoptysis with shortness of breath.

She was first hospitalized in the intensive care for acute respiratory failure (hemoptysis, polypnea and desaturation). She was managed with administration of steroids intravenous associated with non-invasive ventilation.

The patient denied abdominal pain, nausea, vomiting, pruritus, illicit drug use, skin tattoos, blood transfusions, alcohol abuse, recent travel, or multiple sexual partners. She denied any history of liver disease and upper respiratory tract (rhinitis and sinusitis). She has no relevant past medical history. On arrival, the patient was conscious, oriented and pale; oxygen saturation was 90% via face mask 5 L/min, with lower limb edema. Chest examination showed dullness to percussion, decreased tactile fremitus, and asymmetrical chest expansion, with diminished expansion on the side of the effusion. She had a high blood pressure level at 180/90 mmHg, and her pulse was at 104 eats/minute. Cardiovascular, abdominal and neurological exams were unremarkable. The remainder of her physical examination was within normal limits. Laboratory findings showed hemoglobin 7.2 gm/dl, with disturbed kidney functions (creatinine: 394 umol/L), elevated liver enzymes: AST 229 UI/L (normal range < 40UI/L); ALT 206 UI/L (normal range < 40UI/L); total bilirubin 74 umol/L (normal range <17); alkaline phosphatase 484 IU/L (normal range < 290 UI/L); prothrombin 69%. An extensive workup was done to find the etiology of elevated liver enzymes. Only blood work that came back positive was for chronic hepatitis B infection (positive for HBs Ag, HBc IgM, HBe Ab, and positive HBs Ab but with low titer, negative for HBe Ag). Hepatitis B virus load was 4 800 000 IU/mL. Serum protein electrophoresis showed a decreased alpha 1 globulin in favor of hepatocellular insufficiency. The results of serology and immunology showed negative for HIV and other hepatitis. The antinuclear antibodies came back positive one mixed pattern (speckled and nucleolar), anti-smooth muscle antibodies were positive 160 (< 80 UI/ml) with low level titer of antiactine suggestive of autoimmune hepatitis (AIH). The other antibody was negative (anti mitochondrial antibody, anti-liver kidney microsome 1, antiglomerular basement membrane antibody, antidouble stranded DNA, extractable nuclear antigen antibodies). Workup for other causes of vasculitis, including anti-neutrophil cytoplasmic antibodies (ANCA) was positive for c-ANCA antibody to protéinase 3 (3, 0 IU/ml < 2, 0), and negative p-ANCA antibody myeloperoxidase (2, 1 IU/ml IU/ml < 3,5IU/ml). Cryoglobulenemia and blood gas analyses test was not done. Kidney and liver biopsy was unavailable. MRI of the liver was unremarkable. A computed tomography scan (Figure 1) of her lungs revealed features suggestive of bilateral alveolar hemorrhage. The bronchoscopy was not done. Microscopy with gram stain and acid-fast bacilli stain followed by culture did not reveal any organism. Electrocardiogram and echocardiography showed no abnormalities detected. The patient's inflammatory and vasculitis work-up was unremarkable. Malignancy work-up was also negative. Diagnosis of chronic hepatitis B virus was finally established, associated with AIH, end-stage renal disease and alveolar hemorrhage and c-ANCA positive. She was managed for lamivudine® administered orally. The patient was followed for more than one year and there were no other new systematic symptoms, but with the permanent kidney involvement eventually (creatininemia: 287 umol/L) and chronic anemia with blood transfusion).



a b

Figure 1. *Axial CT-scan section of the thorax passing at the height of the hilar region in the mediastinal window (a) showing moderately abundant bilateral pleurisy and in the parenchymal window (b) showing a ground glass condensation (Arrows) with central and perihilar distribution; related to alveolar hemorrhage.*

3. Discussion

This case report describes an atypical case of chronic HBV induced ANCA positive complicated by end-stage renal disease requiring hemodialysis, autoimmune hepatitis and alveolar hemorrhage. Medical investigations allowed excluding other infectious diseases, malignancies and other rheumatic and vasculitis affections. Moreover, borderline positive c-ANCA was significantly higher in chronic hepatitis B group as compared to control [2]. In addition to these manifestations, chronic HBV has also been documented to be involved in the etiopathogenesis of antineutrophil cytoplasmic antibodies (ANCA)-positive vasculitis [2, 8]. HBV is associated with several extrahepatic manifestations including but not limited to serum sickness, polyarteritis nodosa, urticaria, leukocytoclastic vasculitis, and essential mixed cryoglobulenemia. Extrahepatic manifestations due to HBV infection may be attributed to deposition of immune complexes. Deposition of these complexes in small arteries and glomeruli may be responsible for clinical presentations of vasculitis and nephritis [9]. In the literature, a causal relationship has only been firmly established in a few instances of vasculitis, such as chronic HBV infection and polyarteritis nodosa [3]. Autoimmune hepatitis (AIH) is an uncommon chronic liver inflammation with unclear etiology. There are few cases reported for HBV as a possible trigger of this rare disease [10, 11]. In order to diagnose AIH, it is important to exclude other causes of chronic liver disease. Patients with AIH usually have elevated liver enzymes and immunoglobulin G, with elevated anti-smooth muscle antibodies and antinuclear antibodies [12]. A positive association has been demonstrated between AIH and ANCA. A significant number of patients with AIH have been found to be c-ANCA positive, without myeloperoxidase and proteinase 3. The presence of ANCA can support the diagnosis of AIH especially in the absence of other autoantibodies [13].

Besides hepatitis involvement, membranous nephropathy is one of the widely recognized forms of glomerulonephritis associated with HBV infection. Subendothelial and mesangial immune deposits may cause capillary and mesangial injuries with subsequent inflammation and nephropathy [6, 14]. According to a meta-analysis in 2019, HBV infection is possibly associated with a risk of developing reduced glomerular filtration rate in the general population [15]. Renal involvement may occur with HBV infection and usually involves glomerular or vascular injury. Evaluation may detect proteinuria, hematuria and reduction in estimated glomerular filtration rate. The management options include use of antiviral drugs targeting HBV infection with or without concomitant immunosuppressive medication [16]. The same pathogenesis may be used to explain the end-stage renal disease in our case. So, nephropathy can reveal the hepatitis infection. Rheumatic, vasculitis and infectious disease were excluded.

Vasculitis associated with HBV infection has been reported, although rarely, to be responsible for alveolar hemorrhage without cryoglobulinemia. The cryoglobulinemia test was not done. However, the patient did not have any clinical features suggestive of cryoglobulinemia. So, the cause of pulmonary hemorrhage in our case was unclear but may include underlying capillaritis mediated by immune complex deposition. It may play an important role in the pathogenesis of alveolar hemorrhage, indirectly by triggering an immune reaction that damages lung tissue [2, 5]. The diagnosis of alveolar hemorrhage is considered in patient who develop progressive anemia, dyspnea and hemoptysis with alveolar opacities on chest imaging (with density ranging from ground glass to consolidation), that cannot be explained otherwise. However, hemoptysis, a valuable sign is often absent [17]. When pulmonary capillaritis is not secondary to underlying systemic vasculitis; idiopathic pauci-immune pulmonary capillaritis may be considered, with or without ANCA. Treatment of alveolar hemorrhage should target the underlying disorder. In the primary vasculitides, corticosteroids and immunosuppressants, especially cyclophosphamide, are the mainstay of therapy [17, 18]. In 2019, a china study reported a case of 57-year female with diffuse alveolar hemorrhage in a patient with ANCA-associated vasculitis, with dyspnea and hemoptysis. [19]. So, in our case, the immunological phenomenon is further supported by the association of ANCA and alveolar hemorrhage. A local cause of alveolar hemorrhage such as ANCA-associated to vasculitis, systemic lupus erythematosus, drug induced alveolar hemorrhage, tuberculosis, pulmonary embolism, mitral stenosis and Covid-19 were excluded. 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.

In previous study, a case report described a similar case of chronic HBV with ANCA positive induced vasculitis which damage many tissues. The case consisted of a 33 year-old who presented a subarachnoid hemorrhage, acute transverse myelitis, and nephropathy. Immunofluorescent assay showed perinuclear-ANCA (p-ANCA) within range but cytoplasmic-ANCA (c-ANCA) was positive with an endpoint titer over 1:20 [8]. Recently, another case report revealed a rare case of HBV-associated vasculitis presenting with multiple cavitary nodules of necrosis, granuloma, and capillaritis, mimicking

granulomatous polyangiitis in the lung. Corticosteroid treatment led to the resolution of signs and symptoms as well as successful seroconversion [20].

As far as we can tell, there have been no more such cases that have been formally published in sub-Saharan Africa, and this would be the first case reported from Madagascar. Renal and liver biopsy was unavailable in our country. Furthermore, the patient did not have any clinical features suggestive of systemic lupus erythematosus. The presence of chronic HBV with ANCA can exclude granulomatosis with polyangiitis. So, ANCA alone was not sufficient to make a diagnosis of ANCA associated vasculitis. However, the seropositivity for HBV and c-ANCA pointed toward the vasculitis origin of this case and gave a plausible explanation for kidney, hepatic and alveolar involvement.

In this case, bilateral pleurisy may be secondary to end-stage renal disease. A decline of blood hemoglobin level over a few days without hemolysis or any hemorrhage elsewhere should be an alert for alveolar hemorrhage. In our case, it was difficult to distinguish anemia due to alveolar hemorrhage and anemia secondary to end stage renal disease, and might delay the diagnosis of alveolar hemorrhage. Alveolar hemorrhage and bilateral pleurisy could explain the acute respiratory failure. Distinguishing alveolar hemorrhage from other pulmonary manifestations and complications of the underlying autoimmune disease may be difficult, especially given the rarity of alveolar hemorrhage in the chronic VHB.

Furthermore, the use of steroids might avoid minimising multivisceral failure. Low level titer of antibodies such as antinuclear antibody, antismooth muscle antibody, ANCA and liver enzyme might be secondary to the use of intravenous steroids. In fact, managing an autoimmune manifestation of an infectious disease is complex. Although immunosuppressive agents may be needed to control potentially life-threatening autoimmune complications, there is a risk that the infection might get worse. A reasonable approach is first to control the acute autoimmune manifestations of disease with immunosuppressive therapy and then to deal with the underlying infection to prevent relapse.

4. Conclusion

Chronic HBV with extra hepatic manifestations and ANCA vasculitis are exceptional entities. This case report showed the possibility of HBV infection as a cause of vasculitis and multivisceral failure. In fact, this case consisted of the main differential diagnosis of ANCA associated with vasculitis. Physicians have to recognize the possibility of pulmonary, hepatitis and renal symptoms being triggered by HBV infection in a patient who is a chronic carrier. However, the pathogenesis of HBV triggering autoantibodies or autoimmune disease, such as ANCA or ANCA-associated vasculitis, remains unknown. Need more studies to explain its immune-pathogenesis.

Conflict of Interest

The authors declare that they have no competing interests.

Author's Contribution

All authors contributed to project conception and critical review of manuscript. The author (s) read and approved the final manuscript.

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