

Digital Gangrene and Cryofibrinogenemia as the Presenting Signs of Unsuspected B cell Lymphoma in a Hepatitis B Virus (HBV) Infected Patient: a Case Report

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Abstract

The most frequently studied association between a hepatitis virus and Non Hodgkin lymphoma (NHL) has been with hepatitis C virus (HCV). Association with Hepatitis B virus (HBV) is less studied. In this regard mixed cryoglobulinemia (MC) is more commonly associated with HCV than HBV. Still rarer is cryofibrinogenemia in these patients. Lack of symptoms in addition its rarity delays the diagnosis of cryofibrinogenemia and thus the underlying disorders like lymphoma, etc. This case report describes the diagnosis of unsuspected B cell lymphoma in a patient who presented with absolutely no hematological signs and symptoms and underscores the importance of integrated multidisciplinary approach in the diagnosis of such rare presentations of common hematological malignancies.

Keywords: Non-hodgkin lymphoma, Cryofibrinogenemia, Hepatitis B virus

The most frequently studied association between a hepatitis virus and Non Hodgkin lymphoma (NHL) has been with hepatitis C virus (HCV). Interestingly, the finding which led to the extensive study of this association was near 100 % occurrence of HCV positivity in patients with mixed cryoglobulinemia (MC).(1, 2) There are case reports of association of cryoglobulinemia with HBV. Rarer than cryoglobulinemia is the occurrence of cryofibrinogenemia in HCV and especially HBV associated NHL.

In this CASE REPORT, we describe a case of unsuspected B cell NHL presenting as dry gangrene of upper limb digits due to cryofibrinogenemia in association with HBV positivity. A 64 year male and chronic smoker presented with 1 year history of Raynaud’s phenomenon in upper limb. Intermittently, he also had a few episodes of mild epistaxis. His symptoms progressively increased in last 2 months to the extent of complete blackening of almost all the fingers. Physical examination revealed mild pallor, just palpable splenomegaly and non-significant cervical lymphadenopathy. The most striking was the presence of dry gangrene with line of demarcation in the fingers (Figure- 1). Initial

screening investigations revealed (given in table no 1).

With the suspicion of small vessel vasculitis patient was evaluated for ANA, ANCA which came to be negative. Complements were low (C3: 46 mg%, C4: 6.7mg%). Anti-cardiolipin antibody, congenital thrombophilia screen (Protein C, Protein S and Factor V leiden mutation), anti Ro and anti La were negative. Surprisingly patient tested positive for Hepatitis B surface antigen (HbsAg) and negative for anti-HCV antibodies.



Figure- 1. Shows blackish discolouration of all the fingers but the thumbs.

Table- 1. Shows the results of initial investigations.

Laboratory parameters	Values and special comments (If any)
Hemogram	Hb: 9.2 gm/dl TLC: 4500/ μ L with normal differential Platelet: 1.2 lakh/ μ L ESR: 75mm at the end of 1 hr
Renal function tests	Within normal limits
Liver function tests	Total protein: 7.5 gm/dl. Albumin: 2.8 gm/dl Globulin: 4.7 gm/dl.
Lactate dehydrogenase (LDH)	882 IU/L (normal, 313-618 IU/L)
CT Abdomen	Mild splenomegaly and para-aortic lymphadenopathy (5-6 lymph nodes largest of which measured 2 \times 2 cm)

Serology for infection with EBV, CMV, and Mycoplasma was negative. On confirmation, HBV DNA copies were >100,000 IU/ml and HCV copies were undetectable on PCR analysis. In spite having strong suspicion for cryoglobulinemia, work up came negative for the same.

Assays of plasma for the presence of cryofibrinogen were found to be qualitatively positive (i.e. plasma at 4°C for 72 hours).(3)

Meanwhile unlike initial blood smears, the recent smear was reported to have plenty of lymphoplasmacytoid cells for which patient underwent bone marrow trephine biopsy. This showed focal and interstitial infiltrates of lymphoplasmacytoid and plasma cells. These were later proven on immunohistochemistry to be the infiltrates from lymphoplasmacytoid lymphoma (LPL).

One of the few para-aortic lymph nodes which were initially thought to be of doubtful significance was biopsied under CT guidance. This lymph node on histopathology and immunohistochemistry was confirmed to have lymphoplasmacytoid lymphoma. (Lymphoid cells were CD20 positive, VS38 stained plasma cells and plasmacytoid cells. MIB1 proliferation index was 20%).

Serum protein electrophoresis did not show 'M' band and 24 hour urine protein was 200 mg/24 hours with negative immunofixation.

Patient was thus diagnosed to have B cell lymphoma (LPL) with secondary cryofibrinogenemia in association with HBV infection.

Patient is undergoing treatment with the combination chemotherapy for B cell lymphoma along with anti-virals for HBV infection. Nothing much could be offered for digital gangrene as line of demarcation had already set in.

Discussion

The association of NHL with HBV has been studied much less intensively than with HCV. This is somehow surprising because the first report of a positive association between HBV and NHL was published in the same year as the first reports on the HCV-NHL association.(4)

A recently published meta-analysis,(5) gave the odds ratio of 2.56 (95% CI, 2.24-2.92) for the association of HBV with the development of NHL. On the other hand cryofibrinogenemia is a rarely symptomatic disorder that is under recognized due to the infrequency with which it causes symptoms. There are case reports describing the occurrence of secondary cryofibrinogenemia in association with NHL or HBV and HCV.(6, 7) However to our knowledge, this case report of simultaneous occurrence of LPL, secondary cryofibrinogenemia and HBV infection is the first of its own kind. The underlying disorders may not be evident at the time of diagnosis of cryofibrinogenemia, but may become clinically apparent later which has occurred in our patient too.

Cryofibrinogens were first named and described by Korst and Kratochvil in 1955.(8) These proteins are composed of a complex of fibrinogen, fibrin, and fibronectin.(9)

When plasma is refrigerated at 4°C for up to 72 hours, proteins may precipitate (cryoprecipitate). If refrigerated serum and plasma both form a precipitate, then the precipitated proteins are referred to as cryoglobulins. If, however, precipitation develops after refrigeration of plasma only, the plasma precipitate is referred to as cryofibrinogen.

Cryofibrinogens are not present in normal plasma but can be found in the plasma of patients with neoplastic or thrombotic conditions. Cryofibrinogenemia has been reported to occur in association with conditions such as multiple myeloma, carcinoma, leukemia, pregnancy, oral-contraceptive use, inflammatory processes, collagen vascular disease, and diabetes mellitus.(10, 11)

Cryofibrinogenemia has been classified into an essential (primary) and a secondary form. Essential cryofibrinogenemia develops spontaneously in previously healthy persons. Too few cases have been reported, however, to determine the clinical presentation by patient characteristics. Secondary cryofibrinogenemia occurs with a female to male ratio of 1.4 to 1, but with no age or racial predilection.(10, 11) The diagnosis of cryofibrinogenemia is based on clinical findings, histopathology, and the presence of cryofibrinogens

in the patient's plasma. It is important to work up extensively to rule out secondary causes before making a diagnosis of primary cryofibrinogenemia as during the follow up some cases of cryofibrinogenemia that were initially considered as essential actually had underlying secondary causes.(12)

In fact the conditions to be included in the differential diagnosis of gangrenous skin lesions are cryoglobulinemia, cryofibrinogenemia, antiphospholipid antibody syndrome (APLA), thrombotic thrombocytopenic purpura (TTP), purpura fulminans, coumarin necrosis, and cholesterol crystal embolization.(13)

When cryofibrinogenemia is associated with other disease processes, treatment of the underlying disease is often effective in producing a remission. For essential cryofibrinogenemia, treatments include dipyridamole, heparin, warfarin, streptokinase, streptodornase, stanozolol, oral corticosteroids, immunosuppressive therapy, and plasmapheresis,(14) heparin but relapses often occur upon decreasing dosage or discontinuing therapy.(13, 14) Our patient was treated with both oral corticosteroids (as a part of combination chemotherapy for NHL) and anti-virals for HBV infection with therapeutic success. Presently patients plasma does not show cryofibrinogens and NHL shows complete response.(15)

Finally, despite the uncommon occurrence of cryofibrinogenemia as a presenting sign of haematological malignancy, it is important to consider this condition in the differential when lymphoma is a possibility. Of considerable importance is the attention that must be given to the ordering of the proper diagnostic tests required for the diagnosis of this condition, as morbidity-reducing therapies are available.

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