INTRODUCTION

Cryoglobulinemia is a condition characterized by high titers of cryoglobulins and abnormal immunoglobulins in the serum. The protein conformation of cryoglobulins is altered by temperature changes; low temperatures cause a decrease in their solubility leading to their deposition and injury to tissues notably blood vessels, skin and kidneys. There is a close association between hepatitis C infection and vasculitis with arterial and arteriolar intraluminal eosinophilic material, potentially representing cryoglobulin aggregate, as well as inflammatory infiltrates within the vessel walls. Her hospital course was complicated by an acalculous cholecystitis. The auto-antibody profile was positive for anti-proteinase-3, myeloperoxidase, cardiolipin IgG and phospholipid IgG. The presence of non-organ-specific antibodies was reported at a high frequency in cryoglobulinemia associated with hepatitis C genotype 4; this association is uncommon in the United States but prevalent in Egypt. Biomed. Int. 2010; 1: 96-98. ©2010 Biomedicine International, Inc.

Key Words: Autoantibody, cryoglobulinemia, kidney, skin

CASE REPORT

A 58-year-old female Egyptian immigrant presented with a two week history of bullous lesions and bilateral bluish discoloration of her lower extremities. She had a history of DM2, hypertension and hypothyroidism. She was a non-smoker with no significant family and surgical history. The patient immigrated to the United States five months prior to presentation. Upon presentation to the hospital, she had a blood pressure of 108/76, heart rate of 67/min, respiratory rate of 21/min and temperature of 38.8°C. Upon physical examination her mucous membranes were moist, there was no lymphadenopathy, rales, ronchi or wheezing, her abdomen was neither tender nor distended, and her lower extremities had a bluish discoloration and trace edema (Figure 1).

The lesions began as small erythematous patches and progressed to painful blue discolorations over a six week period. She denied recent trauma, fevers or chills. She was examined as an outpatient by a dermatologist two weeks prior to presentation and a biopsy of the skin indicated bullous diabetocorum. Her initial laboratory tests demonstrated pancytopenia (Leukocytes: 3900 TH/mm3 [4.8-10.8 TH/mm3] Hemoglobin: 10.5 g/dL
[12-16 g/dL], Platelets: 77,000 TH/mm3 [130-400 TH/mm3]) and acute kidney injury (admission creatinine: 2.1 mg/dL, baseline creatinine 0.6 mg/dL [0.7-1.5 mg/dL]). The involvement of multiple organs led to vasculitis being the working diagnosis. The autoantibody profile was positive for anti-proteinase-3 (14 U/ml [<6U/ml]), myeloperoxidase (13 U/ml [<6U/ml]), cardiolipin IgG (23 GPL [<10 GPL]) and phospholipid IgG (13 U/ml [<10U/ml]). Negative results were obtained for ANA and cryoglobulins and rheumatoid factor was 141 IU/ml [0-20 IU/ml]. Several complement factors were present at low levels: C3, 52.3 mg/dL [79-152 mg/dL]; C4, 10.5 mg/dL [16-38 mg/dL] and CH50 <10U/ml [31-66 U/ml]. Hepatitis C is prevalent in Egypt and in this context of vasculitis, reactive hepatitis C antibodies were present (genotype 4e and hepatitis C RNA=44300 IU/mL [<50 IU/mL]). Cryoglobulin and cryofibrinogen levels were measured on three occasions with specific instructions on the adequate handling of the specimens and negative results were obtained each time.

Owing to the progression of the skin involvement, the patient underwent plasmapheresis five times and received high dose corticosteroids with an initial improvement in her condition. Skin biopsies confirmed the diagnosis of cryoglobulinemic vasculitis (Figure 2), revealing arterial and arteriolar intraluminal eosinophilic material representing cryoglobulin aggregates, and inflammatory responses within the vessel walls, which are often observed in the skin biopsies of patients with cryoglobulinemia. A renal biopsy was not performed on the patient owing to her poor health.

The discoloration of the patient’s lower extremities (Figure 1) occurred after she immigrated from a hot climate to a cold one, and this could have precipitated cryoglobulinemia. During her 22 days in hospital she presented with characteristics of acalculous cholecystitis, evidenced by pericholecystic fluid, gallbladder wall thickening, absence of gallstones and a positive sonographic Murphy’s sign. Acalculous cholecystitis has rarely been reported with cryoglobulinemic vasculitis. However, a gallbladder biopsy could not be carried out as the patient was diabetic, preventing us from determining whether the cholecystitis was secondary to the vasculitis or due to the patient’s acute illness.

**DISCUSSION**

This case illustrates the difficulty in establishing the diagnosis of cryoglobulinemic vasculitis. Although the sample was processed appropriately, the initial blood test was negative for cryoglobulins but positive for anti-phospholipid antibodies and ANCA. These findings should raise awareness in terms of the clinical diagnosis of cryoglobulinemia as it frequently occurs in patients with chronic hepatitis C infection. Non-organ-specific auto-antibodies can develop in individuals without cryoglobulinemia as well as those presenting with this condition. Several auto-antibodies including anti-nuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (SMA), anti-liver-kidney microsomal type 1 (LKMA1), anti-parietal cell (APCA), antithyroid microsomal (TMA), anti-neutrophil cytoplasmic (ANCA), anti-double stranded DNA (ds-DNA) and
anti-reticulin (ARA) antibodies have been detected in the sera of patients with chronic hepatitis C infection at various levels ranging from 10 to 66%. The presence of non-organ-specific auto-antibodies can be partially explained by antigenic mimicry between the hepatitis C poly-protein and the antigenic targets of these auto-antibodies. The clinical significance of the presence of these auto-antibodies in triggering an auto-immune response is currently unknown.

Cryoglobulins have been detected in patients with different hepatitis C genotypes but they are normally less symptomatic in patients with hepatitis C genotype 1 (prevalent in the United States) than patients with genotypes 4 (prevalent in Africa) and 5. In Egypt, research addressing the association between chronic hepatitis C infection and non-organ-specific auto-antibodies consistently reports a high incidence (more than 75%) of these auto-antibodies in patients suffering from hepatitis C.

CONCLUSION

Detecting cryoglobulins in blood specimens, despite appropriate handling, is currently difficult in a clinical setting. The presence of cryoglobulins can affect the results of several laboratory tests including complete blood counts and the measurement of auto-antibodies. Positive results for various auto-antibodies is frequently a false positive finding in patients with cryoglobulinemia associated with hepatitis C, particularly genotype 4, which is prevalent in Egypt.

AUTHORS’ NOTE

The authors declare that they have no competing interests. Written informed consent was obtained from the patient’s next of kin for publication of this case report and the accompanying images. A copy of the written consent is available for review by contacting the Editor-in-Chief of this journal. MS, NS and AG contributed equally to the review of literature and writing the manuscript. SE was involved in drafting the manuscript and critically revising it for important intellectual content, and has given final approval for its publication.

REFERENCES