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A Bizarre Red Blood Cell Morphology Induced by Cryoglobulinemia in a Case of HCV and B-Non Hodgkin Lymphoma

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Abstract

Cryoglobulins are circulating immunoglobulins or immunoglobulin complexes characterized by reversible cold induced precipitation occurring between 4°C and 37°C. They have been reported in various infectious, hepatic, autoimmune and hematologic diseases (especially multiple myeloma and lymphoproliferative disorders).

Keywords: Cryoglobulins; Immunoglobulins complexes; Hematologic diseases

Introduction

Cryoglobulins are antibodies that precipitate from serum under conditions of cold and resolubilize on rewarming. Cryoglobulins are classified into types I, II, and III on the basis of whether monoclonality and rheumatoid factor activity are present [1]. Type I cryoglobulins are monoclonal but lack rheumatoid factor activity, are associated with certain hematological neoplasms (e.g., multiple myeloma) and often lead to hyperviscosity. In contrast, type II and type III cryoglobulins may be associated with systemic vasculitis. Both are termed mixed cryoglobulins (II and III) because they consist of complexes of both IgG and IgM antibodies. The IgM components in both type II (monoclonal) and types III (polyclonal) possess rheumatoid factor activity. Ninety percent of patients with vasculitis secondary to mixed cryoglobulins are hypocomplementemic, with C4 levels characteristically more depressed than C3. Hepatitis C Virus infection (HCV) accounts for at least 80% of the vasculitis cases associated with mixed cryoglobulins [2].

Case Presentation

A 51 year man with hepatitis C infection and was newly diagnosed as B-NHL, presented to the hospital with peripheral lower limb ischemia and generalized vasculitic rash. Laboratory findings revealed hemoglobin of 8.3 g/dL, platelet count was 710 × 10^3/ul, serum creatinine 1.6 mg/dL with elevated liver enzymes (ALT; 373 u/L and AST; 364 u/L), complement (C3 was normal with decreased C4; <4 mg/dL). Hepatitis C quantitation by polymerase chain reaction was 386.700 Iu/mL. A peripheral smear at room temperature was notable for distorted red cells, morphologically resemble acanthocytes, hemi ghosts and bite cells (A, B, C). Automated platelet count was falsely elevated in comparison to roughly estimated count (710 × 10^3/ul *vs.* 180 × 10^3/ul). Capillary hemoglobin electrophoresis, G6PD, red cell membrane electrophoresis, reticulocytes count, haptoglobin and LDH were ordered to exclude causes of hemolytic anemia that mimic these morphological changes and all were normal. At different light refraction, smear revealed marked background of cryoprecipitate depositing on and distorting the red cell membrane (D). A rapid test was done to identify the presence of cryoglobulin where a bottom layer of cryoprecipitate was extremely obvious in comparison to control sample when plasma incubated at refrigerator (E). A cryocrit test was 8% consistent with the diagnosis. Rheumatoid Factor (R.F) titer was high (40 Iu/mL) together with low C4 characterize mixed cryoglobulinemia (Serum protein electrophoresis revealed a polyclonal band in gamma region).

This case illustrate bizarre red cell morphological changes together with falsely elevated platelet count in presence of cryoglobulinemia with smear findings that raise concern for unstable hemoglobinopathies, G6PD or hereditary red cell membrane abnormalities.

Discussion

Cryoglobulins may precipitate at temperatures less than 37°C; the precipitation temperature is

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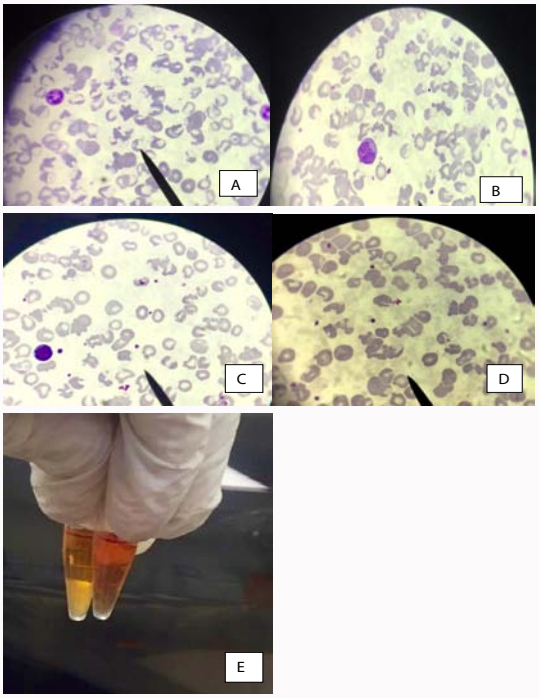

Figures:

highly variable from one cryoglobulin to another. An interference of the presence of cryoprecipitates on blood cell counts is thus likely to occur if cryoprecipitation develops rapidly and at room temperature (18°C to 25°C) [3]. In the above case, cryoglobulins had affected mainly the automated platelet count with falsely high results that on rewarming of the sample, the count was adjusted and confirmed with manual count. It has been reported that cryoglobulins may interfere in White Blood Cell count (WBC) and/or platelet counts, even with current analyzers. The degree of interference in WBC or platelet counts seems to depend not only on the instrument used but also on the type of precipitate. Indeed, spuriously elevated cell counts are due to the presence of particles of cryoglobulin being counted as WBCs or platelets in relation to such physical properties as their size, structure, and shape [4-6].

In the above case, the bizarre and distorting red cell morphology that seen in cases with certain inherited hemolytic anemia and after their exclusion by complete laboratory works, had given a clue for more peripheral smear examination with different light contrast and so cryoglobulins precipitates had been found in the background distorting red cell membranes. A cryoglobulinemia was one of the reasons for the peripheral vasculitis found in that patient with concomitant hepatitis C infection and B-NHL.

Only a few reports on the manifestations of cryoglobulins on blood films have been published [7-9]. Cryoglobulins may sometimes become visible as extracellular that may distort red cell morphology or intracellular material (within neutrophils). Extracellular materials reported are small grayish precipitates fusiform or needle-shaped crystals faintly basophilic or pinkish globules, droplets, flakes, or shapeless aggregates [5].

The present case indicates that significant anomalies in red cell morphology and automated blood cell counts may be related to the presence of cryoglobulin precipitates. The observation of such abnormal histograms must prompt microscopic examination of fresh blood samples and May-Grünwald-Giemsa-stained blood films, which may permit the visualization of specific features of these precipitates. In such cases, the clinician should be informed promptly, as such anomalies may be the first indication of the presence of a cryoglobulinemia.

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