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Pseudoleukocytosis and Pseudothrombocytosis in Cryoglobulinemia

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Abstract: Cryoglobulinemia has been reported rarely to cause false elevation in platelet and/or leukocyte counts due to temperature-dependent protein precipitates that interpreted as blood cells at room temperature. Upon heating to 37°C, these blood counts decrease to normal levels as cryoproteins dissolve. Here, we report two cases with this rare phenomenon that may lead to inappropriate investigations in clinical practice and have diagnostic significance when kept in mind.

Key Words: Cryoglobulinemia, blood cell counts, pseudoleukocytosis, pseudothrombocytosis

Introduction

Cryoglobulins are serum immunoglobulins or immunoglobulin compexes that undergo reversible precipitation at low temperatures. Three main types of cryoglobulins are recognized (1). Type I cryoglobulins consist of a monoclonal immunoglobulin. Type II (monoclonal-polyclonal) and III (polyclonal) cryoglobulins are named as mixed cryoglobulins.

In automated blood cell counting systems, cryoglobulinemia has been infrequently reported to cause falsely elevated platelet and/or white blood cell (WBC) counts due to temperature-dependent protein precipitates that are interpreted as blood cells at room temperature (2-12). Upon heating to 37°C, these blood counts decrease to normal levels as cryoproteins dissolve. Here, we report two patients with cryoglobulinemia, both exhibiting falsely elevated WBC counts and one also with pseudothrombocytosis.

Case Reports

Case 1

A 64-year-old woman had episodically appearing petechia-like eruptions in her trunk and extremities for 6 moths before application (Figure 1). On physical examination widespread, non-bleaching, red, small eruptions that had a tendency to be confluent on some areas were noticed. The eruptions were noticed to increase episodically during hospitalization, mostly after being exposed to cold. The vital signs were normal except mild hypertension (150/100 mmHg). Pallor and pretibial edema were also found. No organomegaly, lymphadenopathy or any other pathological physical finding was present. Complete blood count analyses on different automated particle counters (Coulter S Plus VI, Coulter STKS) revealed leukocytosis changing between 40 x 10^3/µl and 82 x 10^3/µl in different occasions with predominance of the lymphocytes (60 %). Other blood counts revealed normochromic normocytic anemia (6,9 g/dl) with a decreased red blood cell count (2,37 x 10^6/µm), and increased reticulocyte ratio (4 %). Serum haptoglobin concentration was decreased (5 mg/dl, normal range: 30-200). The platelet count was 400 x 10^3/µl. Surprisingly, peripheral smears were not compatible with high WBC counts. Red blood cell clumps indicating presence of a cold agglutinin were noticed. Really, a cold agglutinin was identified at a titer higher than 1:1000. The erythrocyte sedimentation rate was significantly elevated (110 mm/h). Bone marrow smear showed erythroid hyperplasia. No malignant cell was identified. Similarly, no malignant disease could be identified on thoracoabdominal radiological studies and tumor marker analyses. Serological studies for type B and C viral hepatitis, and connective disue disorders, including antinuclear antibodies and antineutrophil cyptoplasmic antibodies, were normal except prominent rheumatoid factor pisitivity (454 IU/ml, normal range: 0-20) that was not accepted as an idicator of any specific rheumatic disease in the absence of arthritis. The 24-hours urinary protein quantification revealed significant proteinuria (2 g/day). In spite of an

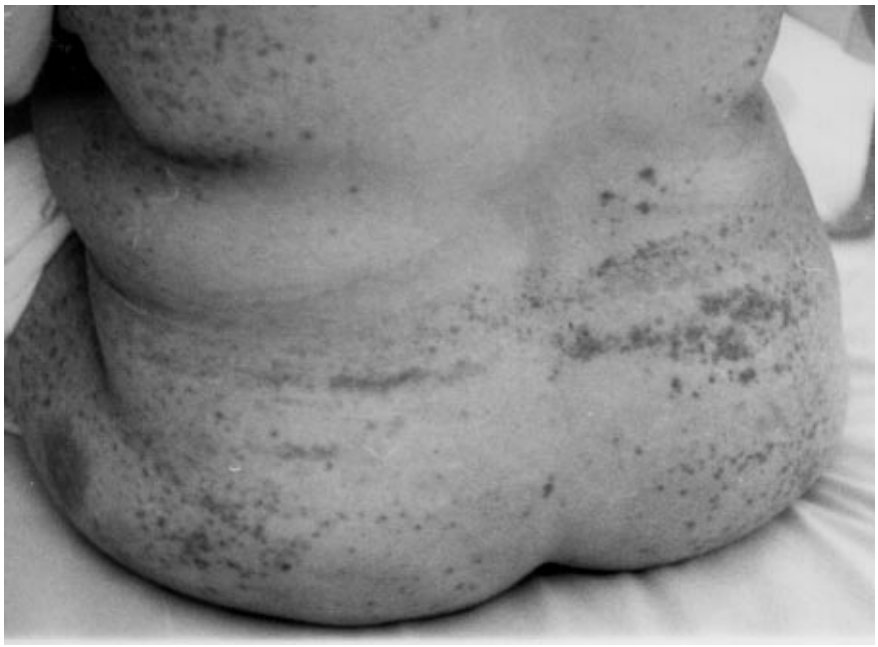

Figure 1. Widespread petechia-like eruptions on the hip and back.

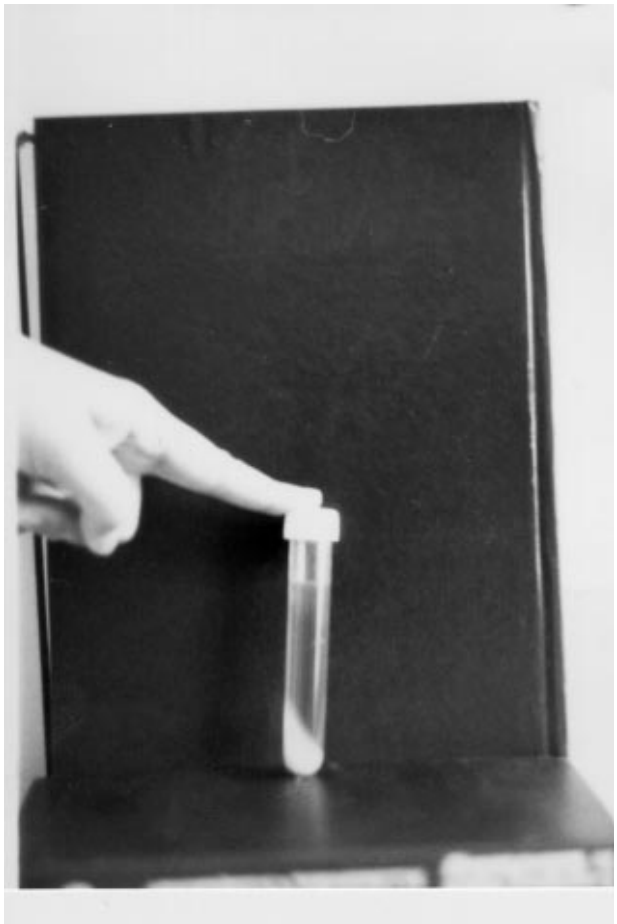

Figure 2. The cryocrit was approximately 12% in Case 1.

active urinary sediment (e.g.red blood cell casts), uremia was not present.

A cryoprecipitate was identified in the serum and analysed with a previously described method (13). Its concentration was 1.47 g/dl. The cryocrit was approximately 12 % (Figure 2). Immunoelectrophoresis of the cryoprecipitate revealed a mixture of monoclonal Ig M K and polyclonal Ig G. Punch biopsy of the skin showed leukocytoclastic vasculitis. Ig M containing depossits were seen in the vessel wall on immunohistochemical studies.

Presuming that falsely elevated WBC counts were due to cryoglobulin precipitates, complete blood count analysis was studied after an incubation period of 30 minutes at 37°C. This time, WBC count became normal (7000/ml). Although therewas a reduction (approximately 50.000/ml) after heating, the platelet count was always within the normal limits. After keeping the same blood at 4°C for a same time or at room temperature for nearly 2 hours, the WBC and platelet counts were again at the basal levels. A WBC count of 21,000/ml and a platelet count of 68,000/ml were present at room temperatur the serum that was collected after 24-hours incubation of the blood at 37°C for cryoglobulin detection.

Four sequences of plasma exchange were performed. Concurrently, a therapy with prednisolon 60 mg/day p.o. (then it was tapered to 5 mg on alternate days) and cyclophosphamide 500 mg per week i.v. (then it was tapered to 500 mg per month) was instituted. Pseudoleukocytosis was not evident 4 months later, when cryoglobulinemia was no more detectable. Vasculitic erup-

tions, rheumatoid factor and cold agglutinin positivites also disappeared and proteinuria decreased to 0,5 g/dl.

Case 2

A 67-year-old woman presented with edema and episodically appearing eruptions in the extremities. These eruptions were identified as palpable purpura on physical examination. No other pathological physical finding other than purpura and edema was present. Some blood count analyses revealed thrombocytosis up to 719 x 10^3/µl and WBC counts high up to 17 x 10^3/µl in her follow-up. Both o f the values werenot compatible with the peripheral smear that was completely normal. The diagnosis of nephrotic syndrome (3.5 g/day proteinuria) and uremia (blood urea nitrogen: 55 mg/dL, creatinie: 2,5 mg/dL) were established. Punch biopsy of the skin showed leukocytoclastic vasculitis. Rheumatoid factor titer was 54 IU/ml. A cryoprecipitate was identified at 0.70 gl/dl concentration in the serum with a cryocrit of 8.5 %. Cryoglobulin immunoelectrophoresis revealed a mixture of monoclonal lg M K and polyclonal lg G. Connective tissue disorders, chornic infectious etiologies including viral hepatitis and malignant disorders were eliminated with a similar diagnostic approach as in the Case 1. Blood count increases were also temperature-dependent. A similar treatment regimen was administered with an identical benefit, i.e. decrease of the cryoglobulin concentration, disappearance of the skin eruptions, but a residual renal failure.

Discussion

These patients had essential mixed cryoglobulinemia type II manifested by vasculitic eruptions and renal disease, the most common clinical presentations of the disease (13,14). All sera from patients with mixed cryoglobulinemia contain rheumatoid factor activity just as in our cases (1). Cryoglobulins may have also a cold agglutinin activity as in the Case 1 (15,16). These laboratory findings not surprisingly may disappear after plasmapheresis or plasma exchange and/or immunusupressive treatment which are the main therapeutic modalities of cryoglobulinemia directed to reduction of the cryoglobulin concentration (13). Recently, it has been suggested that interferon-α is an effective therapeutic agent in essential and hepatitis C-induced mixed cryoglobulinemias (17,18). Removal of the underying disease, e.g. plasma cell dyscrasia, is another treatment strategy that operates in secondary forms of cryoglobulinemia (1).

Falsely elevated blood cell counts due to cryoglobulinemia is a well described, however, still unfamiliar event due to rare occurrence (2-12). Especially, there are very rare records about this phenomenon in the hematological literature (3,4,12). Also, this occurrence is generally not mentioned in the hematology textbooks. Pseudoleukocytosis and pseudothrombocytosis in cryoglobulinemia have been thought to be caused by the cryoglobulin precipitates, which are falsely interpreted as blood cells. The mechanism of these fatuly results in Coulter counters and other instruments using electrical impedance method is increased electrical resistance produced by cryoglobulin aggregates (10). Leukocytosis and/or thrombocytosis that are consistend with peripheral smear findings in a patient with a vasculitic syndrome should be considered strongly suggestive for cryoglobulinemia. A characteristic WBC histogram accompanied by a "warning leukocyte flag" can be seen on the electronic counters in the cases with cryoglobulinemia causing false leukocytosis (12). In order to avoid unnecessary investigations in the patients with vasculitis and suspiciously elevated blood counts, blood cells should also be counted after the blood is heated to 37°C.

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