We report a case of pseudo-thrombocytopenia due to cold agglutinins against platelets. These cold agglutinins were the cause for diagnostic confusion and resulted in extensive workup and unnecessary therapeutic precautions. A thirty two year old female with Guillain-Barre syndrome was admitted in the ICU and serial work-up showed markedly low levels of platelets. The patient had no symptoms of bleeding and patient was investigated extensively for deciphering the etiology of low platelet count. In-vitro clumping of platelets was suspected and in-vitro studies showed marked clumping of platelets with ethylene-diamine-tetra-acetic acid, citrate and heparinized samples. The manual platelet count was found to be within normal limits. Thrombocytopenia as a result of platelet cold agglutinins is a rare cause of in-vitro low platelet counts. No clinical problems have been reported due to the same.

Key words: Cryoagglutinins (cold agglutinins), intensive care units, thrombocytopenia

Introduction

Clinical and laboratory (lab) diagnoses in the intensive care unit (ICU) are challenging. The presence of any lab abnormality triggers further investigations, prolongs the duration of ICU stay and increases health-care costs. This is all the more pertinent when the lab data is a result of an artifact or is due to erroneous factors.

Thrombocytopenia is a commonly occurring situation in the ICU due to a variety of disease or therapy relates causes. However, pseudo-thrombocytopenia is a less known and less reported phenomenon.

We report a case of pseudo-thrombocytopenia due to the presence of cold agglutinins and the diagnostic dilemma that it posed.

Abstract

We report a case of pseudo-thrombocytopenia due to cold agglutinins against platelets. These cold agglutinins were the cause for diagnostic confusion and resulted in extensive workup and unnecessary therapeutic precautions. A thirty two year old female with Guillain-Barre syndrome was admitted in the ICU and serial work-up showed markedly low levels of platelets. The patient had no symptoms of bleeding and patient was investigated extensively for deciphering the etiology of low platelet count. In-vitro clumping of platelets was suspected and in-vitro studies showed marked clumping of platelets with ethylene-diamine-tetra-acetic acid, citrate and heparinized samples. The manual platelet count was found to be within normal limits. Thrombocytopenia as a result of platelet cold agglutinins is a rare cause of in-vitro low platelet counts. No clinical problems have been reported due to the same.

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Case Report

A 32-year-old lady was admitted with a 3 day history of bilateral upper and lower limb weakness. A diagnosis of Guillain-Barre syndrome (GBS) was suspected and patient was shifted to the ICU. The nerve conduction studies were consistent with that of acute motor axonal neuropathy type of GBS. The patient received a 5 day course of intravenous immunoglobulin (Ig). The platelet count at admission was 60,000. The white blood cells and red blood cell (RBC) counts were found to be normal. Repeated counts were on the lower side ranging from 3,000 to 15,000. However, the patient was not symptomatic and had no evidence of bleeding.

Clinical hematologic opinion was sought and a suspicion of sepsis, heparin induced thrombocytopenia, drug/immune mediated thrombocytopenia and dengue were entertained. Accordingly patient was extensively worked up. Immunological work-up including titers of anti-neutrophilic cytoplasmic antibody/anti-nuclear antibody and other investigations such as dengue serology were obtained. However, this extensive work-up did not reveal anything.

A review of the treatment chart was done to exclude any drug induced low platelet count. The patient was on supportive measures and medications as directed by ICU protocol. The patient received ranitidine for stress ulcer prophylaxis and multi-
vitamins. These are not known to cause thrombocytopenia. Noninvasive procedures were undertaken in the interim period and deep venous thrombosis (DVT) prophylaxis with heparin was discontinued in view of the suspicion of heparin induced thrombocytopenia. Mechanical prophylaxis was instituted for DVT.

The hematologist was consulted and it was found that there was in-vitro clumping of platelets with ethylene diamine tetra acetic acid (EDTA). After further discussion and in accordance with the hematologist’s suggestion, EDTA, citrate and heparinized samples were dispatched to the lab. The problem of clumping; however, persisted. The hematologist suspected the presence of cold agglutinins against platelets and analyzed the count by raising the temperature and this revealed a normal platelet count. The count thus obtained was 213,000. The hematologist made a diagnosis of spontaneous EDTA independent platelet agglutination and these platelet cold agglutinins were responsible for considerable diagnostic confusion.

**Discussion**

There are few instances of platelet cold agglutinins reported in the literature. Hayashi et al., reported a case of thrombocytopenia from cold agglutinins. They found thrombocytopenia when the sample was collected with EDTA-2k, MgSO4, citrate and heparin. Flow cytometric analysis revealed the antibody to be of the IgM class. Similarly, Kurata et al., reported four cases of pseudo-thrombocytopenia due to platelet cold agglutinins. The platelet counts in all these four cases were reduced and were in the range of 34,000 to 97,000. The platelets in three of these cases agglutinated below 10°C and in one of them below 24°C. The Ig class in these cases was found to be IgM. The target antigen was found to be the Gp2b3a in two of these instances.

Schimmer et al., reported a case of platelet agglutinins and also an analysis by flow cytometry. In this case, platelet clumping occurred in blood samples taken in EDTA, heparin and citrate containing tubes. In flow cytometric tests, patient serum agglutinated 16% of platelets at 22°C and 7% of platelets at 37°C. In contrast 3% and less than 1% were agglutinated at 22° and 37°C respectively with normal serum. Schimmer et al., also found that addition of monoclonal antiCD41 (Gp2b3a) blocked this clumping effect and less than 2% platelets agglutinated after addition of this monoclonal antibody. The study found the antibody to be of the IgM variety. This did not pose any clinical problems and platelet function as determined by the platelet function tests was found to be normal.

Bizzaro reported a case of pseudo-thrombocytopenia in a patient posted for cardiac surgery. In this patient spontaneous EDTA independent thrombocytopenia was reported due to platelet cold agglutinins. This clumping was produced by the IgM class of antibodies and occurred in the presence of calcium chelating anticoagulants and temperatures less than 37°C. This phenomenon may occur at temperatures as high as 30-33°C. The blood in this case was subsequently collected using the ammonium oxalate and the count was found to be normal and an antiplatelet antibody assay was strongly positive for IgM antibodies.

In our case, the patient was admitted to the ICU with a diagnosis of GBS and the low platelet count was incidentally detected. This spuriously low count however, was the cause of much diagnostic dilemma. It created a diagnostic confusion in the setting of the ICU, which inherently has myriad possibilities. This also led to unnecessary precautions such as avoiding heparin for DVT prophylaxis.

In conclusion, platelet cold agglutinins are a source of much diagnostic confusion. They can potentially increase morbidity and health-care costs and lead to unnecessary and time consuming investigations. The clinical significance of these cold agglutinins and whether they can produce symptoms remains to be determined.

**References**

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