Short Communication

Interventional Cardiology

The COVID pandemic leading to the emergence of a new threat: Cold agglutinin disease

Abstract

As you know Cold Agglutinin Disease (CAD), characterized by the development of autoimmune hemolytic anemia, particularly at temperatures of +4 Celsius, is quite rare. The disease can be asymptomatic, but can also present with clinical presentations that range from anemia, hemolysis-related bilirubinemia, Reynaud's phenomenon, and even organ dysfunction. The pathogenesis is caused by cold-induced autoantibodies against the "i" surface antigen on red blood cells, resulting in agglutination. Cold agglutinin disease is classified as primary or secondary. Secondary CAD is caused by autoimmune diseases, lymphoid malignancy, or infections.

Keywords: Cold agglutinin disease • Coronavirus • COVID • Coronary artery bypass graft surgery • Cardiopulmonary bypass • Agglutination

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Description

The most common pathogens associated with CAD are *Mycoplasma pneumoniae* and Epstein-Barr virus. However, case reports have also associated HIV, rubella virus, influenza virus, varicella-zoster virus, among others [1]. With the recent COVID-19 pandemic, we anticipate that cold agglutinin disease will be much more common with an incidence of one in a million [2]. This is because several case reports have reported that coronavirus causes CAD [3-5]. However, there is currently no research article on this topic as the subject is very new. The increase in incidence of CAD due to the COVID-19 pandemic should particularly concern cardiac surgeons. This is because CAD creates the most fatal complications during cardiopulmonary bypass. Our case of CAD during Coronary Artery Bypass Graft Surgery (CABG), in which the cardioplegia line suddenly clotted and filled with air during the procedure, is a scenario that could happen to any cardiac surgeon. When we saw clots in the cardioplegia line, we checked the heparin drug and Activated Coagulation Time (ACT) and found no abnormalities. We quickly removed the clot from the line and prepared crystalloid cardioplegia and gave it to the patient antegradely. Some clots reached the heart during this time. Additionally, the autologous blood taken by anesthesia had also clotted at +15 Celsius in the operating room temperature and we discarded it without using it. There was no agglutination in the blood in the pump reservoir. This may be because we cooled the patient to +28 Celsius. We could have faced much bigger disasters in deeper hypothermia strategies. Fortunately, in our patient, agglutination occurred only in the cardioplegia line at +4 Celsius and in the autologous blood at +15 Celsius and we were able to discharge the patient without any problems. Another factor that may have prevented cardiac complications in our case is that the antibody-antigen combination that occurs in this disease is reversible and can be resolved when heated. Furthermore, we believe that the air bubbles that occur in the cardioplegia line are caused by the oxygen released from the clotted erythrocytes. And also, the laboratory tests we sent from the patient after the operation showed that only +4 Celsius agglutination occurred,

indicating that the patient had a low-titer CAD is another factor.

After the operation, upon re-taking the patient's CAD-related medical history, we learned that the patient did not have cold-related pain before the COVID-19 infection, but had pain in the auricle and fingertips after the infection. The patient had not felt the need to share this complaint with us during their initial medical history. Considering that the incidence of CAD is likely to increase with the pandemic, routinely inquiring about these symptoms in patients undergoing open-heart surgery with Cardiopulmonary Bypass (CPB) could be life-saving. Furthermore, upon reviewing the patient's previous laboratory tests, we found that after the COVID-19 infection, there was a mismatch between Red Blood Cell-Hemoglobin and an elevation of LDH began.

Performing agglutination tests for the diagnosis of CAD at temperatures up to +4 degrees can be beneficial for patients suspected of having CAD. Our first blood test was conducted at room temperature (+25 Celsius) and the result was reported as negative. If the titer value can be detected after the diagnosis, it is important to determine the titer value. This way, it can be predicted at what temperatures and to what extent the patient will be affected. In addition, hematology consultation is extremely necessary for possible pre- or post-operative treatments and follow-ups and legal responsibilities after the diagnosis of CAD. Using crystalloid cardioplegia instead of bloody cardioplegia or, if possible, completing the surgery with the off-pump technique can be a good solution for CAD. When the incidence of CAD caused by COVID-19 infection is determined by studies, we may need to review our hypothermia strategies in open-heart surgery. Especially moderate and deep hypothermia can lead to fatal results for these patients.

Conclusion

In conclusion, the incidence of CAD is increasing due to the COVID-19 pandemic. Cardiac surgeons should be aware of this growing new threat and include questions related to this disease in their routine questioning of patients and keep CAD in mind when reviewing laboratory results. If the diagnosis is confirmed, reviewing cardioplegia and hypothermia strategies can be life-saving.

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