An unusual cause of heparin resistance - A case report

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ABSTRACT

Primary intestinal lymphangiectasia (PIL) is a rare disorder characterized by dilated intestinal lacteals that result in leakage of excessive serum proteins and lymphocytes into the gastrointestinal (GI) tract culminating in protein-losing enteropathy. The GI loss of protein and possible antithrombin III (AT-III) loss creates a prothrombotic environment. The surgical management of congenital heart disease (CHD) in presence of PIL can present with altered heparin response and can impose problems in instituting cardiopulmonary bypass (CPB). We report a case of surgical closure of ventricular septal defect with PIL with altered heparin response. Such an association of PIL with altered heparin response in CHD has not been reported in literature.

Keywords: Altered heparin response, congenital heart disease, intestinal lymphangiectasia

INTRODUCTION

Altered heparin response is not uncommon in congenital heart disease (CHD), and the incidence varies over a wide range from 4 to 26%. The ideal minimal and targeted activated clotting time (ACT) still remains elusive as there is a wide variation in institutional practice. AT-III deficiency congenital or acquired has been implicated as the commonest cause of altered heparin response. Though extensive evaluation of biological defects in congenital AT-III have been done, the physiological and clinical consequences of acquired AT-III largely still remain unclear.

Primary intestinal lymphangiectasia (PIL), a cause of protein losing enteropathy (PLE), is characterized by dilated intestinal lymphatic structures leading to excessive protein and lymphocyte loss in gastrointestinal (GI) tract. The proposed hypercoagulable state in PIL leading to venous thrombosis and embolic events is attributed to the intestinal loss of coagulation factors and AT-III. Though no direct association of PIL and CHD has been established nor altered heparin response in such a case has been described in literature, its concurrent presence may need careful consideration prior surgery to avoid any mishap during CPB.

CASE REPORT

A 6-year-old male child weighing 15 kg with the diagnosis of ventricular septal defect with mild aortic regurgitation following right coronary cusp prolapse was admitted for surgical repair [Figure 1a and b]. The past history revealed history of abdominal distension, chronic diarrhoea, pedal oedema, and recurrent carpopedal spasm. The blood
investigations showed normal hemogram with normal renal function tests. The liver function test demonstrated total protein 3.6 gm/dl with serum albumin 1.6 gm/dl. The liver enzymes and coagulation profile were normal. The child was diagnosed with intestinal lymphangiectasia following duodenal biopsy. The child was managed conservatively with 20% albumin infusion, injection cholecalciferol along with oral calcitriol, calcium and magnesium supplements. The serum albumin improved to 2.4 gm/dl prior admission.

During surgery, systemic heparinization was initiated with a dose of 500 U/kg and ACT at 3 minutes was measured as 286 seconds. A repeat dose of 400 U/kg heparin improved the ACT to 305 seconds. A total of, 200 ml of fresh frozen plasma (FFP) was infused; however, the ACT was still subtherapeutic (265 seconds). Further dose of 300 U/kg heparin achieved an ACT of 501 seconds. CPB was instituted, and routine VSD closure was done. ACT measured after half an hour of CPB was 414 seconds, and hence additional dose of 300 U/kg heparin was repeated that improved the ACT to 470 seconds. VSD closure was proceeded accepting slightly lower ACT with a short cross clamp time of 35 minutes and CPB time of 57 minutes.

DISCUSSION

Heparin exerts its anticoagulant effect by binding with AT-III, which is an endogenous glycoprotein produced by the liver. Heparin potentiates the action of AT-III 1000-fold on thrombin by forming an irreversible Heparin-ATIII-thrombin complex.[1]

PIL leads to a prothrombotic hypercoagulable state. Various mechanisms for such a physiological milieu have been postulated. The excessive enteric loss of albumin and AT-III along with the immunodeficiency state in the presence of an acute phase reactant protein is the widely accepted hypothesis.[4] Also, significant decrease in the AT-III level is noted when albumin level is <3 gm/dl.[4]

The major consequences following such a state leads to an increased thrombotic risk with altered heparin response. Isolated case reports of incidence of arterial and pulmonary thrombosis requiring higher doses of heparin in PIL have been documented.[6,7] Left-middle cerebral artery stroke in a PIL patient[8] further strengthens our suspicion that patients with PIL do exhibit an altered heparin response.

The preoperative goal in this subset of patient should be directed toward improving serum albumin to normal range that also normalizes the AT-III level.[5] The serum transferrin has a similar short half-life as AT-III and can be a useful monitor to assess the AT-III level following nutritional support.[9] Dietary modification with medium chain triglyceride diet (MCT) forms the mainstay of therapy along with calcium, vitamin D, and fat soluble vitamins supplementation.[9,10] Octreotide has also been used with success in some cases. Selective cases with very low albumin and the AT-III level may require preoperative therapy with AT concentrate based on AT activity. However, with good nutritional status, most of the cases can be managed with fresh frozen plasma to supplement AT-III for altered heparin response.

To conclude, altered heparin response should be anticipated in cases of PIL and should be managed aggressively with nutritional supplementation in order to prevent possible altered heparin response encountered during CPB. A larger group of patient with PIL/PLE should be evaluated with the AT-III level to further establish this association.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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