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Case Report
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Development of a Recurrent Pulmonary Embolism During the Post-Coronary Artery Bypass Grafting Surgery (CABG) Period in a Patient with Previous History of Unusual Coincidence of Pulmonary Embolism, and Drug-Induced Cold Agglutinin Haemolytic Anaemia Disease Following an Elective Total Knee Joint Replacement Surgery

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Abstract

I describe an interesting case report of a middle-aged male patient with a background previous history of unusual coincidence of pulmonary embolism, and drug-induced "cold agglutinin haemolytic anaemia disease" following an elective total knee joint replacement surgery, developing a recurrent episode of pulmonary embolism during post- coronary artery bypass surgery period. The case illustrates the point that exercising a high degree of suspicion in diagnosing pulmonary embolism following cardiac surgery should be of paramount importance. The current case also appears to be unique, and extraordinary in the sense that the unusual coincidence of pulmonary embolism, and "cold agglutinin haemolytic disease" in this previously healthy patient had occurred following his total knee joint replacement surgery. I have extensively documented the relevant subject matters concerning the etiology, pathogenesis, diagnosis, and treatment/management of the above- mentioned haematological disorder/complication in the context of post operative cardiac surgery period in the case report.

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Introduction

I describe an interesting case report of a middle-aged male patient with a background previous history of unusual coincidence of pulmonary embolism, and drug-induced cold agglutinin haemolytic anaemia disease following an elective total knee joint replacement surgery, developing a recurrent episode of pulmonary embolism during post-coronary artery bypass surgery period.

Case Presentation

A 70 year old male patient with a background history of previous episodes of gradually worsening angina pectoris, and exertional dyspnoea, despite optimal medical therapy, in the context of underlying triple vessel coronary artery disease, presented to the "Accident and Emergency" (A&E) department on 14th February, 2011, with an episode of sudden onset central retrosternal chest pain of approximately one hour duration, radiating to the left arm, and associated with diaphoresis. The ECG monitor demonstrated transient ST segment elevation on the lateral leads, associated with a raised Troponin level, confirming the diagnosis of ST Elevation Myocardial Infarction (STEMI). Subsequently, the patient was admitted to the hospital under the Cardiology team, and treated initially medically by the cardiology team with administration of Heparin, intravenous GTN infusion, in addition to Aspirin. The coronary angiography conducted on 8th November, 2010, had demonstrated evidence of triple vessel coronary artery disease with well preserved left ventricular function.

His significant past medical/surgical history had included a post-operative pulmonary embolus (fourth day post op) in the context of epidural anaesthesia, and absence of any Heparin

thromboprophylaxis following an elective total knee joint replacement in 2002. Shortly after the development of his post knee surgery pulmonary embolus, his post operative recovery had also been complicated by the development of respiratory tract infection treated with Co amoxiclav, and new onset of anaemia associated with a raised blood unconjugated bilirubin level, and an elevated blood reticulocyte count of 9%. Direct antiglobulin test had been found to be positive for complement, and suggested a diagnosis of "cold agglutinin haemolysis disease" in the context of low titer mycoplasma antibodies in the blood, and the administration of Co amoxiclav immediately preceding the haemolytic disease. His bone marrow smear had demonstrated erythroid hyperplasia with no evidence of any excess of lymphocytes and no other malignancy. Bone marrow trephine biopsy had not shown any lymphoid infiltrate. The haematology team had decided to treat his haemolytic anaemia by commencing the patient on Folic Acid, and maintaining his body temperature sufficiently warm at that time, in addition to Manuscript (title page, abstract, ultramini, text, tables) blood transfusion. The patient had also received Warfarin therapy for six months for his post knee surgery pulmonary embolus.

Following his admission to the hospital in February, 2011, with acute onset angina pectoris, and STEMI, the Cardiology team decided not to undertake any primary PCI (Percutaneous Coronary Intervention) on the patient, and referred the patient to the Cardiothoracic Surgical team for an urgent "Coronary Artery Bypass Grafting" (CABG) surgery. The patient eventually underwent an urgent on-pump CABG × 3 procedure uneventfully, under the Cardiothoracic Surgical team on 16th February, 2011. From the very first post operative day, the surgical team commenced administering regular oral Aspirin, prophylactic dose of subcutaneous "Low Molecular Weight Heparin" (LMWH), and graduated compression stockings, in addition to other cardiac medications. On the second post operative day following CABG, he required re-endotracheal intubation and ventilation for respiratory insufficiency complicated by respiratory tract infection associated with a raised blood CRP level, and low grade pyrexia. However, the patient was haemodynamically stable, and was commenced on intravenous antibiotics (Teicoplanin, and Meropenem) for his respiratory tract infection. His blood haemoglobin level on the second post operative day also decreased quite significantly down to 7.0 gram/deciliter, from a pre-CABG blood haemoglobin level of 14.0 gram/deciliter, requiring blood transfusion. There was no objective laboratory evidence of any cold agglutinins in his blood specimen at that point in time. On the third post operative (CABG) day, he developed a moderate sized right sided pleural effusion requiring a right sided intercostal chest drain using a Seldinger type pigtail chest drain. The culture examination of the microbiology specimens turned out to be negative. Subsequently, the patient was extubated successfully, and transferred back to the surgical ward in a stable haemodynamic status with no evidence of any major respiratory insufficiency. His blood haemoglobin level also continued to improve gradually over the next few days following his initial blood transfusion. On the fifth post CABG day, his hepatic function test results did not demonstrate any evidence of any bilirubinaemia/jaundice. On the ninth post CABG day, the patient experienced an episode of acute hypoxaemia associated with a right sided pleuritic type chest pain, tachypnoea, dyspnoea, sinus tachycardia, decreased arterial blood PO2, and decreased air entry into the pulmonary bases bilaterally on auscultation. The chest XRAY conducted urgently demonstrated non-specific atelectatic changes involving the pulmonary bases bilaterally. In view of his previous episode of PE post knee surgery in 2002, an urgent CTPA (CT Pulmonary Angiogram) scan of the thorax was conducted in order to rule out any evidence of any acute PE. The CTPA demonstrated acute or chronic pulmonary embolism with evidence of pulmonary embolus in main left superior lobe pulmonary arteries, and segmental divisions of the right middle, and inferior lobar pulmonary arteries, associated with bilateral emphysematous changes, and lower pulmonary lobe consolidation/collapse. Following the detection of his acute pulmonary embolism, the patient was immediately warfarinized with a target blood INR range of in between 2.0 and 3.0, in addition to intense chest physiotherapy, and regular nebulizer therapy for his bilateral pulmonary atelectasis. There was no evidence of any acute haemolytic anaemia at that point in time. Subsequently, the patient managed to achieve a satisfactory recovery, and was discharged from the hospital on 3rd March, 2011. The patient continued to recover well following his discharge from the hospital, and was eventually discharged from the Cardiothoracic Surgical out-patient clinic back to his General Practitioner's care on 3rd May, 2011, following a satisfactory systemic review.

Discussion

Deep Venous Thrombosis (DVT) and PE occur less frequently following cardiac surgery than after other major surgical procedures owing to the use of anticoagulant medications during cardiac interventions [4]. Nevertheless, asymptomatic venous thromboembolism occurs following CABG with surprisingly high frequency (15% to 20%), and the incidence of PE following CABG ranges from 0.5% to 4% [1]. Quite understandably detection rate for symptomatic VTE in the inpatients following CABG tends to be low. Dr. Samuel Z. Goldhaber has reported 1% incidence of symptomatic Venous Thromboembolism (VTE) following CABG, with 50% of all cases of DVT- irrespective of the symptoms-occurring in the leg contralateral to the great Saphenous vein harvest site, and 84% of all cases turning out to be distal DVTs. Dr. Goldhaber has estimated that the mortality rate was 1% in the asymptomatic patients, and 2% to 4% in patients with symptoms of VTE, in post-CABG scenarios [2]. However, the hospital mortality rate in cases of massive fatal PE can range from 43% to 80% within the first two hours, with 85% of the patients succumbing to the massive PE within the first six hours [3].

Pulmonary complications that can occur following cardiac surgery include pulmonary atelectasis, pleural effusion, pulmonary edema, acute respiratory distress syndrome, pulmonary embolism, sepsis, and diaphragmatic dysfunction [4].

The diagnosis of post CABG pulmonary embolism can often be quite difficult as symptoms such as shortness of breath (Tachypnoea/dyspnoea), alterations in blood oxygen content, sinus tachycardia, and pedal oedema can easily be ascribed to post-surgical changes in relation to deconditioning pulmonary atelectasis, and/or underlying left ventricular dysfunction. Differential diagnosis for this type of symptomatic presentation following cardiac surgery could also have included pericarditis, costochondritis, surgical wound related complication, or, anxiety. Undoubtedly some of the patients who 'die suddenly' within 30 days of CABG succumb to PE without any clear/specific warning signs, and without the diagnosis of PE being established [2]. The case illustrates the point that exercising a high degree of suspicion in diagnosing PE following cardiac surgery will be of paramount importance.

Risk factors for the development of PE following cardiac surgery

include heparin induced thrombocytopaenia (18% patients) and previous thromboembolic disease (21% patients) [4,5]. Current thromboprophylaxis measures following CABG are predominantly based on passive and active mobilization, graduated compression stockings, use of antiplatelet therapy, and administration of fixed low-dose subcutaneous unfractioned heparin or "Low Molecular Weight Heparin" (LMWH) [6]. Aspirin used universally following CABG may have a very weak but measureable effect in reducing the frequency of post operative VTE [7].

Graduated compression stockings are relatively inexpensive, and free of any serious side effects. Graduated compression stockings increase venous blood flow and prevent peri-operative venodilation in the lower limbs [2]. Intermittent Pneumatic Compression (IPC) devices generate intermittent inflation of air filled cuffs preventing venous stasis in the lower limbs, and creating compression over the veins more forcefully than the graduated compression stockings, in addition to stimulating the endogenous fibrinolytic system [8].

In the case being presented, the patient was commenced on both LMWH (prophylactic dose, subcutaneous administration) and oral aspirin during the immediate post-CABG period, in addition to the application of compression leg stockings. Despite the institution of all those preventative measures in the immediate post-CABG period, the patient subsequently developed an acute episode of PE on the ninth post-operative day. This case event emphasises on the fact that more clinical trials should be conducted in VTE prophylaxis among patients undergoing CABG with a previous history of PE. In addition to the LMWH, the role of novel anticoagulants such as fondaparinux (A direct factor Xa inhibitor), and Ximelagatran (An oral direct thrombin inhibitor) needs to be established for the prevention of VTE in patients undergoing CABG. The results of those trials will contribute to the reduction in mortality, morbidity, and healthcare expenditure in terms of reduced hospital stay.

Cold agglutinin haemolytic anaemia disease represents a form of haemolytic anaemia in which high concentrations of circulating antibodies, predominantly IgM variety (90%), have been found to be directed against red blood cells at reduced body temperatures, typically in between 28°C and 31°C. Primary/idiopathic cold agglutinin disease does not have any recognizable cause, whereas the secondary form of the disease can result from other conditions, including lymphoproliferative disease (Lymphoma/chronic lymphoid leukemia), Mycoplasma pneumonia, mononucleosis, HIV, and sepsis. Since cold agglutinin disease is mediated by an IgM molecule in 90% of patients, and the IgM molecule has got a molecular weight of approximately one million Daltons (1000 kD), the molecular size can span the intercellular distance between red blood cells; agglutination can be noticed at 4 degrees Celsius in the microtiter well without the use of any antiglobulin antisera. The IgM antibodies resulting in haemolytic disease can be polyclonal, post-infectious, or monoclonal, the classic cold haemagglutination disease. Management of cold agglutinin induced autoimmune haemolytic anaemia may well be a therapeutic challenge, especially in a post-operative setting [9].

The current case also appears to be unique, and extraordinary in the sense that the unusual coincidence of pulmonary embolism, and "cold agglutinin haemolysis disease" in this previously healthy patient following his total knee joint replacement surgery in 2002. During his post-CABG recovery period, the patient did not demonstrate any objective clinical evidence of any haemolytic anaemia, and his microbiology culture results, including blood culture result, turned out to be negative without any detection of any Mycoplasma species. However, reactivation of the cold agglutinins associated with complement activation at subclinical level triggered by the decrease in his body temperature to 32°C during institution of the cardiopulmonary bypass for CABG, and also induced by his pulmonary sepsis during the early post-CABG period could well have contributed, to a certain extent, to the development of the second acute episode of pulmonary embolism in this patient despite institution of thromboprophylaxis.

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