HYPERFIBRINOGENEMIA AND SEVERE CARDIOVASCULAR DISEASE A CASE REPORT

JAHANGIR AHMED BUKSH, MRCP(UK); MUSSAAD M.S. AL-SALMAN, FRCS; MOHAMMED R. ARAFAH, FRCP; MOHAMMED M.S. NOUH, MD; ABDULKAREEM AL-MOMEN, FRCP

INCREASED LEVEL OF CERTAIN HEMOSTATIC FACTORS play an important role in the causation of cardiovascular disease. High fibrinogen level is believed to be a major risk factor for cardiovascular disease, peripheral vascular disease and stroke.1-5 A single episode of thromboembolic phenomenon in young patients needs to be thoroughly investigated for assessment of hemostatic risk factors. This report describes hyperfibrinogenemia in a young patient complicated by severe cardiovascular disease.

Case Report

A 34-years old Egyptian male, a heavy smoker for 16 years, presented to King Khalid University Hospital, Riyadh, in March 1998, with pain in the right calf and ulceration of right big and second toes of one year's duration. He had been admitted to a local hospital in Egypt previously, with a diagnosis of thromboangitis obliterans (Buerger's disease), with gangrene of right big and second toes. The affected toes were partially amputated with no symptomatic relief. After two months he had attended a hospital in Riyadh, where lumbar sympathectomy with complete amputation of right big and second toes was performed without any relief of his symptoms. In addition to pain and extension of gangrene involving right foot, he developed impotence. The patient was then referred to vascular unit at King Khalid University Hospital for further investigations and management.

On examination, his blood pressure was 120/80 mm Hg. Radial pulse rate was 90 per minute, with irregular rhythm. Also, pulses in the right lower limb were absent. Systemic examination was unremarkable. Local examination of right foot revealed amputated big and second toes and gangrenous right foot.

Laboratory investigations revealed WBC of 3.6 x 10^9/L, hematocrit (Hct) 35%, platelets 342 x 10^9/L and an ESR of 35 mm in the first hour. Biochemical work-up including fasting blood sugar of 6 mmol/L; blood urea, 6 mmol/L; serum creatinine, 110 ~mol/L; serum cholesterol, 4.5 mmol/L; serum triglyceride, 1.6 mmol/L; total serum protein 68 g/L; serum albumin, 34 g/L; and liver function tests were within normal limits. Ultrasonography of abdomen did not reveal any abnormality.

A recurrent non-sustained ventricular tachycardia was detected on telemetry (Figure 1). However, ECG did not show any significant ischemia. Resing dypridamole thallium imaging revealed reversible perfusion defects in the inferior and septal areas. Coronary angiogram showed subtotal obstruction with multiple filling defects in the right coronary artery. Left coronary artery system was normal (Figure 2). Aortogram performed for the assessment of arterial system of lower limbs showed a complete obstruction of the right superficial femoral artery from its origin to the popliteal artery and its bifurcations. Left lower limb arteriogram was normal (Figure 3).

A complete hematological work-up of the patient was performed to investigate the recurrent thromboembolic phenomenon. Increased level of
serum fibrinogen at 8 g/L (normal range is 2.5 g/L to 3.5 g/L) was detected. Prothrombin time and partial thromboplastin time were normal. No evidence of infection, inflammation or malignancy was found. A preliminary diagnosis of chronic persistent hyperfibrinogenemia was made after exclusion of other contributing factors such as protein C activity, protein S activity, anti-nuclear antibody, antcardiolipin antibody, syphilis serology and antithrombin III activity.

The patient was treated with heparin infusion, oral warfarin and amiodarone. Since the requirement of warfarin was high, bezafibrate in the dose of 200 mg thrice a day was instituted. Bezafibrate was well tolerated and a significant reduction in serum fibrinogen level (from 8 g/L to 2.4 g/L) was achieved over a period of two weeks.

Femorotibial bypass graft surgery was advised. Thrombotic occlusion of venous systems of both lower limbs confirmed by duplex study rendered the patient unfit for bypass graft surgery. A right leg below knee amputation was performed after two months of conservative management. Biopsy specimens were taken from veins, nerves, arteries and muscles during the surgery. Except for the thrombotic occlusions of arteries and veins, no other pathology was reported (no histological evidence of disease). The patient was reviewed in the hematology outpatient clinic every two months for a period of nine months before he left the Kingdom for good. He remained well in his follow-up regarding his cardiac status, however, serum fibrinogen level remained elevated (4 g/L to 6.2 g/L) despite treatment.
Persistently elevated serum fibrinogen level is emerging as a strong and a prognostically significant risk factor for coronary artery disease, stroke and peripheral vascular disease. Serum fibrinogen level has been shown to be positively correlated to the extent and severity of coronary artery disease. It is, therefore, logical to suggest that the longer the exposure to elevated serum fibrinogen, the higher the chance of developing associated complications. Being an acute phase protein, a variety of stressful conditions may increase plasma level of fibrinogen transiently. In this patient, gangrene of the right foot could have contributed to the increased level of serum fibrinogen. Hyperhomocysteinemia may also present with thromboembolic phenomenon, and could have been a possible diagnosis. Laboratory investigations were not performed due to the lack of facilities. This patient presented with most of the thromboembolic phenomenon in warfarin-resistant cases. Bezafibrate has been shown to potentiate the hyperfibrinogenemia. There was no previous action of warfarin. The patient has been well and no documentation of increased serum fibrinogen levels, as further episodes of thromboembolism have occurred during the hospital admissions. Diagnosis of hyperfibrinogenemia was made as serum fibrinogen level was high on admission and remained elevated on follow-up despite treatment. The primary diagnosis of this patient was thromboangitis obliterans (Buerger's disease). It is a bilateral inflammatory occlusive vascular disorder involving small and medium-sized arteries and veins of the upper and lower limbs distally. Involvement of cerebral, visceral and coronary arteries may be a feature of thromboangitis obliterans. The clinical presentation of thromboangitis obliterans and hyperfibrinogenemia may therefore overlap. There was, however, no histopathological evidence supporting the diagnosis of thromboangitis obliterans in this patient.

Hyperfibrinogenemia is a controllable risk factor. Elevated serum fibrinogen level can be reduced by regular exercise, giving up smoking and weight reduction. This patient was a heavy smoker and cigarette smoking has shown to increase the risk of atherosclerotic coronary artery disease and peripheral vascular disease. The relationship of cigarette smoking to the occurrence of atherosclerotic cardiovascular disease could be attributed to the high serum fibrinogen level. The elevated serum fibrinogen level can thus be controlled effectively by avoiding factors contributing to elevated serum fibrinogen levels.

Pharmacological agents, e.g., heparin, anccord, bezafibrate, danazol, ticlopidine and low-dose urokinase, have been shown to effectively control serum fibrinogen level. When this patient was treated with bezafibrate (200 mg, t.i.d.), a dramatic fall in the serum fibrinogen level was observed in two weeks, from 8 g/L to 4.2 g/L. Bezafibrate failed to bring the serum fibrinogen level to normal level, which remained between 4 g/L to 6.2 g/L on repeated assessment during the follow-up period of nine months. It is, therefore, suggested that bezafibrate though effective in reducing serum fibrinogen levels, fails to bring serum fibrinogen levels to within normal limits. A combination of warfarin and bezafibrate may be an effective drug therapy for the reduction of recurrent thromboembolic phenomenon in warfarin-resistant cases. Bezafibrate has been shown to potentiate the hyperfibrinogenemia. The patient has been well and no further episodes of thromboembolism have occurred despite persistent, elevated serum fibrinogen levels.

Acknowledgment

The author gratefully acknowledged thoughtprovoking discussions with, and technical support by Dr. Zahid Shakoor.

References


