Case Report

Leukemoid like reaction in a post CABG patient

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ABSTRACT

The presentation of leukemoid reaction in patients post-cardiac surgery is rare with limited prior reports in the English language literature. We report a case of raised leukocyte count with no evidence of infection in a patient post coronary artery bypass graft surgery. The exaggerated inflammatory response by the patient to extra-corporeal circulation was drastically elevated, but fell short of the leukaemoid reaction definition – so we have defined it as a leukaemoid like reaction. A clear correlation between the extra-corporeal circulation and inflammatory response is documented.

Key words: Extra-corporeal circulation, leukaemoid reaction, leukotrienes, myelogenous leukaemia

INTRODUCTION

A reactive leucocytosis, with a significant increase in early neutrophil precursors, exceeding 50,000/mm^3 is referred as leukaemoid reaction.[1] These reactions are generally benign, but may imitate more serious conditions such as chronic myelogenous leukaemia.[2] Leukemoid reaction may be a paraneoplastic manifestation of several cancers such as lung, gastrointestinal, genitourinary, ovarian, head and neck cancers and hepatocellular carcinoma.[3,4] Non-cancerous conditions that can precipitate a leukemoid like state include those of situations of stress, infection and inflammation. These reactions have been attributed to increased cytokine production.[5] The cytokines implicated in this process include granulocyte-macrophage colony-stimulating factor (CSF), granulocyte-CSF (G-CSF), interleukin-3 (IL-3) and IL-6.[6,7]

CASE REPORT

A 54-year-old female with angina (NYHA-class II), double vessel disease (left main coronary artery equivalent, distal left anterior descending artery - 95%, distal circumflex artery - 80%) with good left ventricular (LV) function was referred for coronary revascularisation. She was otherwise well except for a recent history of type 2 diabetes mellitus. Physical examination was unremarkable. Pre-operative investigations revealed a white blood cell (WBC) count of 12,900/cmm (neutrophils 61%, monocytes 6% lymphocytes 29% eosinophils 4%) and urinalysis was within the normal limits. The raised total leukocyte count (TLC) was possibly attributed to her type 2 diabetic status, the radial artery angiogram procedure that was done 2 days prior to the pre-anaesthetic check-up and possibly to the recent angina that the patient had at the time of admission (1 week).[8] Although she remained asymptomatic an early coronary artery bypass grafting (CABG) was planned. CABG was performed using the left internal mammary artery and left great saphenous vein graft. Cardiopulmonary bypass (CPB) time was 110 min with aortic cross-clamp for 58 min, using antegrade cold crystalloid cardioplegia. The patient came off CPB easily and remained haemodynamically stable thereafter. She was ventilated overnight and extubated. Post-operatively (on the day of surgery) routine blood tests demonstrated a mild leucocytosis (20,900/cmm)

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with marked neutrophilia (71%), lymphocytosis (20%), and monocytosis (9%). She had normal chest X-ray and urine analysis results. The patient remained asymptomatic in spite of the increase in the leukocyte count. On the first post-operative day the TLC increased to 25,000/cmm and to 29,500/cmm on second post operative day. This increasing trend in the WBC prompted us to change the antibiotic from first line antibiotics (cefuroxime + ofloxacin) to second line antibiotics (cefoperazone + sulfactum + ofloxacin) assuming a subclinical infection due to her diabetic status. The patient remained asymptomatic with no signs suggestive of sepsis. Platelet counts were within normal limits. Blood, urine and sputum culture showed no growth of organisms after 48 h. Laboratory work-up for infective (bacterial and parasitic) aetiology revealed negative results. The usual cardiac supports were tapered off on the third post-operative day and the patient shifted to intermediate care unit on the fifth day in spite of her rising total WBC count. The WBC count reached 33,000/cmm on the third day and 41,000/cmm on the 4th post-operative day without any signs of infection.

On the fifth post-operative day the TLC increased to 49,400/cmm (neutrophils 54%, lymphocytes 30%, and monocytes 16%). Inflammatory parameters were mildly elevated (C-reactive protein [CRP] 38 mg/L). A peripheral smear showed marked leucocytosis, predominately neutrophils and mild shift to left was noted with presence of myelocytes and band forms. Reactive lymphocytes were also seen. Red blood cell (RBC) were chiefly normocytic, with increased polychromasia and occasionally normoblast. Platelets were adequate in number. Serum procalcitonin to rule out sepsis was not assessed as the patient was clinically stable with mildly elevated CRP levels and also keeping in mind the limited resources, the cost factor and delay in reporting.[9-11] Chest X-ray and ultrasound abdomen did not reveal obvious causes of possible solid viscera tumours that can cause a leukemoid reaction. Computed tomography (CT) of chest, abdomen and pelvis were postponed, to be obtained at review.

On 10th post-operative day the TLC was 43,500/cmm. Thus a provisional diagnosis of leukemoid like reaction - post CABG surgery was made and patient discharged on the 10th post-operative day with an advice for follow-up 1 week later. The TLC was 15,000/cmm with neutrophils 68%, eosinophil 2%, monocytes 6%, and lymphocytes 24% on her next visit which confirmed the diagnosis of leukaemoid like reaction.

DISCUSSION

Leukaemoid reaction was first reported by Krumbhaar in 1926.[12] Leukocytosis exceeding 50,000 WBC/cmm with a significant increase in early neutrophil precursors is referred to as a leukaemoid reaction. In most cases a leukemoid reaction has an underlying medical disorder which triggers the elevated WBC count. There are many possible causes of leukaemoid reactions. Certain types of chronic infection such as mononucleosis, malaria, and tuberculosis, certain types of cancers, Hodgkin's disease and autoimmune anaemia may cause leukemoid reactions [Table 1]. Thus it is a clinical syndrome in which changes are found in the peripheral blood similar to what occurs in people with leukaemia, but not the result of leukaemic disease.[13] Leukaemoid reaction has also been reported to occur in allergic reaction of phenobarbital, an aromatic anticonvulsant drug[14] [Table 1].

In our patient, the possible cause of the raised TLC with monocytosis during the pre-operative time would

Table 1: Common causes of leukaemoid reaction

Infections	Shigellosis
	Hepatic abscess
	Tuberculosis
	Sepsis
Paraneoplastic	Bronchus carcinoma
	Carcinoma of bladder, kidney and prostate
	Carcinoma of tongue and nasopharynx
	Carcinoid
	Hepatocellular carcinoma
	Carcinoma of oesophagus
	Cholangiocarcinoma
	Carcinoma of cervix or ovary
	Splenic haemangiosarcoma
	Liposarcoma and soft tissue sarcoma
	Leiomyosarcoma of the bladder
	Melanoma
	Bone metastasis
	Multiple myeloma
	Hodgkin's disease
Drug Induced	Granulocyte colony stimulating factor
	Corticosteroids
	Tetracycline
	Streptokinase
	Carbamazepine
	Thiopentone Sodium
Miscellaneous	Diabetic ketoacidosis
	Alcoholic hepatitis
	Ethylene glycol intoxication
	Enteric necrosis

have been due to the angina pectoris, which she had at the time of admission. The radial angiogram would also have contributed in the rise of the TLC. The study by Maekawa *et al*. showed that the peak monocyte count had a significant positive correlation with LV end-diastolic volume obtained from pre-discharge left ventriculography. Patients with pump failure or LV aneurysm had higher peak monocyte counts than those without these complications. Multivariate analyses showed that a peak monocyte count 900/cmm was an independent determinant of pump failure, LV aneurysm and long-term adverse cardiac events.[8]

Post CABG our patient presented with a rise in TLC which was due to increased neutrophil count along with relative lymphocytosis and monocytosis. The possible causes resulting in the scenario could be malignancies (carcinoma, plasma cell myeloma, or lymphoma), chronic infections or autoimmune disorders. All laboratory work-up for acute and chronic infective (bacterial and parasitic) aetiology revealed negative results. Blood peripheral smear showed marked leucocytosis, with predominately neutrophils with presence of myelocytes and band forms. Reactive lymphocytes were also seen. RBC were chiefly normocytic normochromic with increased polychromasia and occasional normoblast. Thus the peripheral smear showed leucoerythroblastic blood picture with reactive lymphocytes. Thus a bone marrow study was required to rule out any blood related dyscrasia. The other possible reason for this abnormal behaviour may be due to inflammatory response to the extra-corporeal circulation. Studies have proved that after revascularisation the total blood monocyte counts tend to rise temporarily, peaking between day 2 and 3 after intervention.[15] This monocytosis may be related to the process of healing and LV remodelling. The resident macrophages in the myocardium are activated and synthesize and secrete humoral factors that cause monocytopoiesis.[8]

Cardiac surgery produces an altered activation of the inflammatory response due to the combination of surgical trauma, CPB and ischemia-reperfusion injury.[16] Marked amplification of this process may result in SIRS. In the case of our patient, it appears that the inflammatory storm generated by cardiac surgery with CPB precipitated a dramatic myelomonocytic leukemoid reaction, with no clinical picture of SIRS and multiple organ dysfunction syndromes.[17]

The question that arose was why our patient responded to the inflammatory stress of surgery in such an unpredictable fashion. Our prime suspect was that of undiagnosed underlying chronic myelomonocytic leukaemia (CMML) or any other malignancies, which may progress to the acute phase of leukemoid reaction, a complex and poorly understood response by the bone marrow to stress. In this patient, it appears that the inflammatory storm generated by cardiac surgery with CPB precipitated a dramatic myelomonocytic leukemoid like reaction. A leukemoid reaction may rarely prove rapidly fatal although the cause of disease acceleration and potential remitting factors remain obscure.

Our patient was planned for a later bone marrow biopsy to exclude leukaemia and finally demonstrated a lack of myeloid clonality. Thus with the provisional diagnosis of leukaemoid reaction, investigations such as bone marrow biopsy, LAP score and CT thorax abdomen pelvis were deferred in consultation with the physicians and surgeons. A review with TLC and dendritic cell was planned a week later. Investigation of the bone marrow including immunophenotyping could have helped us to differentiate between leukaemia and a leukaemoid reaction. LAP scoring could confirm our provisional diagnosis, while CT thoracoabdominopelvis can help to rule out solid tumours that commonly produce leukaemoid reaction.

Not much is known about the incidence and course of leukaemoid reactions. Most knowledge is based on case reports.[18] A paraneoplastic leukaemoid reaction can be caused by increased serum levels of G-CSF or other growth factors, which are considered to be produced by the malignant cells, mostly from an endothelial tumour. The leukaemoid reaction can be present even years before the diagnosis of the carcinoma.[19]

The only report of off-pump CAB in a patient with CMML, performed via a median sternotomy, highlighted concerns over leukaemoid transformation and the assumed benefits of a reduction in cytokine release.[20]

CONCLUSION

A clear correlation exists between the extra-corporeal circulation and inflammatory response. When WBC counts increase grossly, a cause outside the bone marrow has to be searched for. The leucocyte count was showing increasing trend throughout the post operative period after CABG in the present case and no clear

source could be found, including sepsis and hence, we termed it as leukaemoid (WBC count >50,000/cmm) like reaction.

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