ARTERIAL THROMBECTOMY IN CANCER PATIENTS

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There is a strong relation between hypercoagulopathy state and malignancy. In various tumors, coagulation system activation may be encountered to different extents. Moreover, cytostatic drugs increase the incidence of thrombosis. In Cerrahpaşa School of Medicine, Thoracic and Cardiovascular Surgery Department, 4 patients underwent operations upon due to acute arterial occlusion during chemotherapy. These cases are reviewed in the view of literature. In our study the aspects of arterial thromboembolism in cancer patients are emphasized. The need for high dose anticoagulant and the high insidence of rethrombosis are pointed out.

Key words: acute arterial occlusion, hypercoagulopathy, arterial thrombectomy

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Cardiopathy is the most common cause of arterial embolization. Malignancy is also an infrequent cause of arterial thrombosis or embolization. There is an important relationship between hypercoagulopathy and malignancy. Activation of coagulation is evident in various types of tumors. Threaupeutic agents also induce thrombosis. On the contrary, hypercoagulable state associated with cancer could be the cause of bleeding, related to disseminated intravascular coagulopathy. The outcome of arterial thrombectomy in cancer patients depends on the hemotological status of the patient.

The first succesful embolectomy was performed by Georges Labey in 1911. Major advances in the management of arterial embolism were achieved by the introduction of anticoagulant agents in 1940 and the introduction of baloon catheter by Fogarty et al. in 1963. Despite the improved technique of embolectomy, the outcome of an embolectomy may not always be predictable [1]. This report is aimed to clarify the effect of cancer on thromboembolism and outcome of operations performed.

CASE REPORT

Case 1. A female patient, 65 years of age, was referred to our clinic because of acute brachial arterial occlusion while receiving chemotheraphy. By routine physical examination, right upper extremity was pulseless entirely, painful and cold. Ascites was present, an epigastric mass was palpable, and collateral circulation was apperent in the umbilical area. She had no cardiac murmur and arrhytmia with auscultation.

In abdominal CAT scanning; invasion of the pancreas and gastrocolic ligament was present, peritoneal carcinomatosis and retrovesical metastatis was detected. In addition, enlargement of the celiac and diaphragmatic lymphatic ganglions were recognised. The clinical manifestations, evaluation and additional problems determined the patient as grade 4 gastric carcinoma. On the first day of chemotherapy, treatment consisting of 5-fluorouracil and cisplatin, acute arterial occlusion of the right upper extermity was aroused as a complication.

Thrombectomy of the brachial artery was carried out immedeately. Postoperatively all arterial pulses were present. Heparin infusion (1000 unit per hour) was begun. However , on the second postoperative day rethrombosis occured again and the patient was reoperated. Activated coagulation time (ACT) was below the therapeutic level thus, heparine dose was elevated up to 2000 unit per hour. The possibility of a subclavian artery aneursym was considered. Arterial angiography was obtained, but no evidence of subclavian aneursym and atherosclerotic changes of the luminal surface were detected. Four days after the second operation, oral anticoagulation was began, and continous heparin infusion was stopped after determination of prothrombin levels between the therapeutic ranges. Brachial thrombosis reoccurred. Third thrombectomy was performed from the same incision. We continued heparin infusion as 2000 U per hour. Fourth thrombectomy was performed and this time, 1 cm. of the brachial artery was resected and anastamosed end-to-end because of iatrogenic intimal lacerations.

Postoperatively heparin dose was elevated up to 3000 U per hour, and lowered to 1500 U per hour two days later. Coumadin was began in addition to heparin treatment. Three days later heparin was stopped. At the night of heparin cessation the clinical status of the patient has changed abruptly, and within minutes the patient died.

Case 2. A 23-years-old woman was referred for brachial occlusion to our clinic. She had been diagnosed as acute lymphocytic leukemia and chemotherapy had been begun. After the last chemotherapy consisting of vincristine, daunorubicin and prednisone, brachial thrombosis of the right upper extremity occured.

On physical examination all arterial pulses of right upper extremity were absent distal of the axillary artery. She hadn't any underlying disease which can cause systemic thromboemboly such as atrial fibrillation, vetricular aneurysm or any other cardiac disease. She had anemia and thrombocytopenia. Brachial thrombectomy was performed. Postoperatively heparin infusion treatment 1000 U per hour was began. Reoccurance became evident after ten hours, and the patient was reoperated. Angiography of the subclavian artery did not demonstrate any pathology. The heparin infusion rate was elevated up to 2000 U per hour. Meanwhile ACT and aPTT levels were detected. After four days thromboemboli reoccured and the third thrombectomy was carried out. Postoperatively the patient was followed in the intensive care unit. Levels of ACT and aPTT were measured frequently and heparin treatment was altered depending on these measures 60.000 U/h heparin was given. Three days after coumadine treatment was began according to PT levels, and the patient was discharged.

Case 3. A male patient 53 years of age with adenocancer of unknown origin, brachial occlusion developed on the left upper extremity while receiving the fourth chemotherapy comprising; cisplatin, mitomycine, cyclozozamide and cortisone. On physical examination all arterial pulses of the left extremity were absent. The patients history did not reveal any evidence of

thromboembolic disease, or any problem related to vascular pathology. His cardiac status was normal. X-ray examination of the lungs demonstrated multiple metastasis of an unknown origin. In addition metastasis of the vertebra and of os ischiadicus was recognized in CT scan.

Brachial thrombectomy was performed. Postoperatively all pulses were present. Heparin infusion treatment 1000 U per hour was given. Next night it was seen that pulses were absent. Reoperation was undertaken. At operation, thromboembolic material couldn't be extracted by fogarty catheter. It was noticed that viscosity of blood was increased and there was a low grade inflow but thromboembolectomy couldn't provide adequate flow. An associated preexisting arterial lesion was suspected. Angiography was performed. Stenosis at the origin of the subclavian artery and thromboembolus of the brachial artery was demostrated.

The patient was operated. The subclavian artery was mobilized and its branches were ligated and divided. Also the subclavian artery was divided and third thrombectomy was performed. Thereafter the subclavian artery was anastomozed to the common carotid artery. Postoperatively heparin administration wasn't continued. Four days later acute occlusion of the brachial artery emerged. All peripheral pulses distal to the axillary artery were absent. Fourth thrombectomy was required. The patient was heparinized according to ACT and aPTT. After the coumadine dosage was scheduled the patient was discharged. Duration of hospitalization was one mounth.

Case 4. A 65-year-old female with non hodgkin lenfoma was referred for thrombectomy of the right upper extremity. After receiving the fifth chemotherapy consisting of; Endoxan, Adriamycine, Oncovine and Prednol, acute arterial thrombosis of the brachial artery was developed.

On physical examination bifurcation of the brachial artery was occluded, ulnar and radial arterial pulses were absent. Her cardiac status was normal, and she hadn't had any evidence of thromboembolism.

Arterial thrombectomy was undertaken. Postoperatively heparin infusion 2000 U per hour was administered for three days and anticoagulation therapy began.

On the sixth postoperative day she was discharged.Complication didn't emerge in follow up.

DISCUSSION

An association between thromboembolic disease and cancer was suggested by Arnold Trousseau in 1865 [2]. Since then vascular thrombosis has been recognized as a complication of cancer. Clinical manifestations associated with malignancy are arterial and venous thrombosis, migratory thrombophylebitis, pulmonary embolism, onbacterial endocarditis and paradox bleeding [2,3]. The incidence of TED (thromboembolic disease) in patients with cancer has been reported to vary between %1 and %11[4]. The incidence of TED in postmortem studies of cancer patients is considerably higher [5]. Some types of cancer are more thrombogenic than others. In general, lymphoproliferative disease rarely provokes thrombosis. However, adenocarcinomas of abdominal organs such as pancreas, stomach and biliary tract are more prone to thromboembolic complications. Some small cell carcinoma of the lung is also frequently complicated by thrombosis [3].

As seen in Table 1, the incidence of TED is higher in lung tumors. In the last five years 170 patients who had lung tumor were operated in our unit, and any evidence of clinical TED was not recognized. In the same period 193 patients underwent arterial embolectomy. Four of the 193 cases were associated with cancer, and all occured during or after chemotherapy in the brachial artery. The incidence is 2.07%.

Clinical studies have shown that migratory thrombophelibitis, deep vein thrombosis and pulmonary embolism may occur before malignancies [6,7]. Any kind of TED before or after the diagnosis of cancer has not been recognized in our cases.

A retrospective clinical evaluation of vascular trauma as a result of therapeutic procedures

Table 1. Distribtion of tumor types in 541 cases of cancer associated with clinical thromboembolic disease.

Tumor Type	Number of cases	Frequecy (%)
Lung	139	25.6
Pancreas	94	17.4
Stomach	91	16.8
Colon	82	15.2
Prostate	35	6.5
Ovary/Uterus	34	6.3
Gallbladder	15	2.8
Breast	11	2.0
Kidney	2	0.4
Other and unknown primary	37	7
Total	541	100

for the treatmentt of malignancy showed that, sixteen of 22 vascular injuries were caused by intraarterial administration of chemotherapy. Eight of the cases were arterial emboli [8]. In a study 6.8 % incidence of thromboembolism during chemotherapy was reported and the significant relation between the risk of thrombosis and age was emphasized. Among the patients over 50 years old, the incidence of thrombosis during chemotherapy was seen higher (10.3 %). In this clinical study all thromboembolic events occured during drug therapy, and none during follow-up without chemotherapy [9]. As seen in our cases all of them were receiving chemotherapy when the sudden onset of symptoms began. Case 3 may be controversial but the subclavian artery stenosis had been present in the past. Therefore it is not difficult to attribute recurrent thromboembollism to cancer and chemotherapy. The mechanism of the thromboembolic effect of anticancer drugs is still unknown. It was suggested that chemotherapy reduces fibrinolytic activity, and cytotoxic drugs damage endotelial cells [9]. Abnormalities of routine tests of blood coagulation have been reported to occur in as many as 92% of patients with cancer. The most common clotting abnormalities in cancer patients are elevated levels of fibrin/fibrinogen degradation products, thrombocytosis, and hyperfibrinogenemia. These abnormalities, overcompensated intravascular coagulation with fibrinolysis, have been said to be consistent with the presence in cancer patients [3].

An increased rate of fibrinogen and plasma levels of fibrinopeptide A (FPA) have been observed in virtually all patients with acute leukemia and solid tumors [10]. FPA levels appear to reflect clinical responses in cancer patients, suggesting a dirct relationship between tumor growth and thrombin generation [11]. Yedulman and colleagues noted that patients who developed TED as a complication, failed to normalize their plazma FPA levels in response to the intravenous administration of heparin [12]. Conventional anticoagulant therapy may be refractory in some patients as case 1.

The activation of clotting system is brisk and sustained, DIC can occur with severe hypofibrinogemia and diffuse bleeding [13]. In Case 1 one week after the last operation heparin treatment was stopped. At night of the heparin cessation alterations in consiousness, headache, nausea and vomiting began. Within few minutes the patient became comatose and died suddenly. The clinical presentation was evaluated as cerebral hemorhage.

Though prolongation of prothrombin time is mentioned in the literature, prothrombin time of our patients were normal. So as to reach a prolonged prothrombin time, we used high doses of heparin. We recommend high dose heparin infusion after arterial thrombectomy in cancer patients.

CONCLUSION

The management of a cancer patient with an arterial thrombosis has been a challenging problem for the vascular surgeon. Although arterial thrombosis is not infrequent if arterial route is used for administration of chemotherapy, it is a rare condition ancountered in cancer patients. The hypercoagulable state in cancer is the main reason of thromboembolism. After occurence of TED in cancer patients, resistance to heparin treatment may emerge. The outcome

of the patient after embolectomy varies according to various parameters. Consequently surgeons should evaluate all criteria that can effect the survey of the patient and the underlying disease carefully.

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