Arterial Thrombosis Associated with Malignant Disease

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Objective. The association between cancer and venous thrombosis is well established, however, that between malignancy and arterial thrombosis is less well described. Isolated cases have been reported and chemotherapy has been implicated as a cause though its significance compared with the malignant disease process itself is not known. This study examines the outcome of patients with malignant disease who present with arterial thrombosis.

Method. Details of patients with malignant disease who presented with arterial thrombosis were analysed.

Results. Twenty patients presented with malignancy and arterial thrombosis, 16 presented in the last four years. The most common malignancy was metastatic breast cancer. Thrombosis involved the leg in 19 cases and the arm in one. Four patients also had venous thromboembolic events and one had a carotid artery thrombosis. Eight patients underwent operative treatment for their thrombosis. Five out of six thromboembolectomies and two out of three bypass procedures failed. Twelve had conservative or palliative treatment. Outcome was generally poor, two patients had major amputations and seventeen died at median follow-up of eight weeks. Survival rate from the time of presentation of arterial thrombosis was 50% at three months and 17% at one year.

Conclusion. Patients with critical limb ischaemia due to atherosclerotic disease have an expected survival of approximately 80% at one year. The outcome of patients with arterial thrombosis associated with malignant disease is far worse. Arterial thrombosis is an agonal event in many of these patients. Conservative or palliative treatment may be the most appropriate management.

Keywords: Thrombosis; Arterial; Malignant disease.

Introduction

Venous thromboembolism is found at post-mortem in at least 50% of cancer patients. There is an overall 7-fold increased risk of venous thrombosis in patients with malignancy compared with people without malignancy. A recent study analysing the risk of possible underlying malignancy in patients with venous thromboembolism detected malignancy in 10 out of 126 (7.9%) patients with idiopathic deep venous thrombosis (DVT). Arterial thrombosis in these patients has not been widely described.

There are fewer than 50 cases of spontaneous arterial thrombosis with no iatrogenic or atherosclerotic cause in cancer patients reported in the literature. There are isolated case reports and two studies. The first study looked at a series of 311 patients with pancreatic adenocarcinoma, two (0.006%) of whom developed arterial thrombosis. In the second, 192 consecutive patients presenting over 18 months with critical limb ischaemia (CLI) were analysed and investigated for markers of occult malignancy. Of these 22 (11.5%) were confirmed to have an underlying cancer. Ten presented with acute ischaemia and 12 had chronic ischaemia. The difference between the groups was not significant.

Pathogenesis of thrombosis is complex and multifactorial in patients with malignant disease. Thrombosis may be iatrogenic, related to vessel catheterisation, surgical interventions or adjuvant treatments. It may be related to the underlying neoplastic process. Adjuvant therapy and the paraneoplastic process lead to a hypercoagulable state with changes in levels of Factor VII and proteins C and S. Tissue factor and cancer procoagulant levels may rise. Thrombocytosis, increased fibrinogen levels and reduced fibrinolysis, endothelial damage and stasis may also precipitate thrombosis.

Major vascular reconstruction may not be appropriate if both the patient’s prognosis and the outcome of surgery are poor. Prognosis of patients with
malignant disease who present with arterial thrombosis is poorly documented. The aim of this study was to examine the outcome of these patients.

**Method**

A prospective study of patients presenting with arterial thrombosis who had an underlying malignancy was carried out. All such patients were included who presented to a vascular unit at a District General Hospital. Patient demographics, medical history, presentation and outcomes were recorded. Kaplan-Meier plots were used to analyse the amputation rate and patient survival.

**Results**

**Demographics**

Twenty patients, thirteen women and seven men presented. Sixteen patients presented in the last four years. Median age was 63 years with a range of 35 to 86. Nineteen presented with acute thrombosis. Twenty-two limbs were involved. The majority of patients (19) presented with thrombosis involving the leg; one involved the arm. Two patients had evidence of thromboses in both legs. Three patients had a past history of leg ischaemia, two with intermittent claudication secondary to peripheral vascular disease (PVD). One underwent angioplasty 18 months previously. One patient presented with acute limb ischaemia 6 years previously requiring embolectomy. Of those without a history of PVD six were smokers and one had had a cerebrovascular accident six years previously.

**Malignancy**

The types of cancers, their adjuvant treatment and outcome are shown in Table 1. Five patients also had a history of a primary cancer of a different origin than their present malignant disease. Twelve patients had metastatic disease. Sixteen patients had been treated with some form of adjuvant therapy, nine within a month prior to their presentation with arterial thrombosis. Three had had both chemotherapy and radiotherapy.

Four patients presented with venous thromboembolism either shortly before or after the arterial event. Three of these had recurrent venous thromboses. One patient with a leg DVT was later found to have internal jugular vein and superior vena cava thromboses. The other two had bilateral leg DVTs, one of whom also had a splenic infarct and pulmonary embolus. One patient had pulmonary emboli two months after his presentation with arterial thrombosis.

**Treatment**

A decision was made to manage four of the patients with palliation only as they were moribund and their condition deteriorated rapidly. Four others were treated conservatively with anticoagulation, glyceryl trinitrate patches and analgesia. Chemical sympathectomy was performed in two cases. The remaining 12 had angiography. Four of these were treated conservatively and eight surgically; all were given anticoagulation. Five had thromboembolectomies, one bilaterally. In three thrombectomy was not possible and they had bypass procedures.

**Outcome**

Five of the six thromboembolectomies failed, four within 24 hours and one at three weeks. The remaining patient had some initial improvement but then deteriorated and died six weeks later. Three thromboembolectomies were repeated, two of these failed. One went on to have a below-knee amputation and died five months later. Limb survival is shown in Table 1.

Table 1. Type of cancers in patients presenting with arterial thrombosis and number of patients who received adjuvant therapy prior to their arterial presentation and outcome

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<th>Lung Adenocarcinoma</th>
<th>Adenocarcinoma unknown primary</th>
<th>Colorectal</th>
<th>Breast</th>
<th>Leukaemia</th>
<th>Transitional cell carcinoma</th>
<th>Ovarian Squamous cell carcinoma</th>
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Fig. 1. The other was treated with streptokinase which failed and she died three weeks later. Of the three bypass procedures two failed within six weeks. The first, who underwent an ileofemoral and femoropopliteal bypass had further thromboses and died six weeks postoperatively. The second, a femoro-femoral crossover graft, had a graft thrombosis two weeks post operatively and required an above-knee amputation but died a week later. The third who underwent a femoropopliteal bypass died six months postoperatively.

During follow-up period seventeen patients died. Median survival was 2.5 months [Table 1 and Fig. 2]. Ten patients (seven men) who died had metastatic disease. The age range of those who died was 43—86 years with a median of 67. Of those who died 13 had received adjuvant therapy, six less than a month prior to their arterial event and nine in the previous three months. There was a 50% survival at three months and 17% at 12 months [Fig. 2].

Of the three survivors one had adenocarcinoma of unknown primary origin and two had breast cancer. Two had metastatic disease. The median age in this group was 51 with a range of 35—72 years. Of these one had chemotherapy within a month of their arterial thrombosis and two had both chemotherapy and radiotherapy. Only one of the survivors had been treated surgically. One patient went on to have a non-fatal carotid artery thrombosis 16 months after presentation with limb thrombosis.

Discussion

This study demonstrates the poor outcome of patients presenting with arterial thrombosis when an underlying malignancy is present. Two patients (10%) underwent major amputations, both within a month. By contrast, the amputation rate at one year of patients with critical limb ischaemia due to atherosclerosis is 12%. The survival rates of our patients are low compared with patients presenting with critical limb ischaemia due to atherosclerotic disease. Eighty three percent of our patients died within one year compared with 80% survival at a year in PVD patients with CLI. Over 95% of claudicants are alive at one year. Our results are comparable to those in the two studies previously mentioned. Schattner concluded that arterial thrombosis is a terminal event in patients with pancreatic cancer. In El-Sakka’s study half of the patients died within six months.

These patients with widespread malignancy have a poor prognosis. The additional insult of arterial thrombosis appears to be an agonal event in most cases. In managing these cases consideration needs to be given to the likely outcome. This study is the only case series defining the outcome of such patients. Postoperative outcome is poor. Seven out of nine thromboembolectomies failed as did two of three bypass procedures. The patient with the successful bypass died six months postoperatively. Only one of the eight patients who underwent an operation survived. El-Sakka et al. suggested thromboembolectomy or angioplasty offers palliative treatment. Angioplasty was not appropriate in any of our cases and we have shown that attempts at revascularisation are unlikely to be successful. Repeated attempts may be required and are likely to fail. Although not used in our study thrombolysis is an alternative non-invasive treatment.
option. Its feasibility has been written about in sporadic reports in the literature. The combination of streptokinase and urokinase transcatheter infusions has been shown to be more effective than either alone.11 Though patient numbers are low our results suggest a conservative approach may be the most acceptable. The severity of ischaemia caused by the thrombosis may dictate whether anticoagulation or palliative support only is more appropriate. Campbell discusses the dilemmas involved when making these difficult decisions and advises palliative care in advanced cases when acute limb ischaemia is just one part of a terminal illness.12 Of our patients two of the eight treated conservatively survived. The six who died had an average survival of 33 weeks.

The type of cancers involved was varied and no conclusion can be made as to the types most likely to present with arterial thrombosis. Malignancies associated with the highest risk of venous thromboembolic disease are haematological, lung and gastrointestinal.2 The debate as to whether extensive screening for malignancy is necessary in patients with idiopathic DVT continues. A moderate screening strategy is recommended by Oktar et al.,3 which includes simple laboratory tests, chest radiography and abdominopelvic ultrasonography. It is not so clear whether screening patients with idiopathic arterial thrombosis is necessary. The most common cancer in El-Sakka’s study was lung cancer and they have recommended routine chest radiography in all patients with CLI.5 However, the range of cancers in our series was so varied that any single investigation cannot be recommended as a screening. Most of our patients did not have a history of PVD and many had no risk factors for thrombosis. It could be argued that occult malignancy should be suspected in those in which arterial thrombosis presents in the absence of precipitating factors. Rigdon and Mark et al.14 recommend investigation for occult malignancy where no biochemical evidence of a hypercoagulable state or history of PVD exists. The most common cancer in our study was breast cancer. This may be related to the common use of adjuvant therapy in these patients. One study showed that premenopausal breast cancer patients are more likely to present with arterial thrombosis if they have received both chemotherapy and tamoxifen compared with chemotherapy alone.15

The significance of adjuvant therapy in the pathogenesis and outcome of our patients is unclear. All three of the survivors and only six of those who died had had adjuvant therapy in the month prior to their arterial presentation.

Five of our patients suffered other thromboembolic events other than their primary presentation with peripheral arterial thrombosis. One developed carotid artery thrombosis and four had venous thromboembolic events. There are reports in the literature of cancer patients developing both arterial and venous thromboses.13,16 It is surprising that the recording incidence is not higher. It may be that many venous thromboses remain undiagnosed.

Conclusion

Acute arterial thrombosis in the presence of active malignancy carries a very bleak prognosis. The outcomes from surgery are poor. Careful consideration of palliative care may be appropriate as arterial thrombosis is an agonal event in many.

References


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