NOTE Internal Medicine

Unilateral Femoral Arterial Thrombosis in a Dog with Malignant Mammary Gland Tumor: Clinical and Thermographic Findings, and Successful Treatment with Local Intra-arterial Administration of Streptokinase

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ABSTRACT. An 8-year-old intact female dog presented with a sudden onset of unilateral hindlimb paralysis of 3 days duration. Based on the history and results of physical, neurological, and histopathological examinations, and blood work, an arterial thrombosis was suspected as a complication of the hypercoagulability from a malignant mammary gland tumor. Thermography provided evidence of the unilateral femoral thrombus. Initially, thrombolysis with streptokinase administered by intravenous infusion was ineffective. Thereafter, the direct delivery of streptokinase to the site of thrombus was attempted. The approach was curative. These results suggest that thermography could describe the site of the arterial thrombus, and local intra-arterial administration of streptokinase may be an effective therapy for the canine arterial thrombosis complicated by malignant mammary gland tumor.

KEY WORDS: arterial thrombosis, canine, mammary gland tumor, streptokinase, thermography.


Thrombosis is the intravascular deposition of fibrin and platelets that can lead to an ischemic condition. Cancer-related hypercoagulability can induce thrombosis and is thought to initiate a cascade of events that lead to the constriction of collateral vessels [18]. Human studies [1, 2, 21] have demonstrated that the incidence of thrombosis is high in adenocarcinomas. In veterinary medicine, a recent study of 60 dogs with mammary carcinoma correlated with the frequency and intensity of coagulation parameter abnormalities with tumor progression [19]. However, the incidence of thrombosis was not reported. In general, non-selective angiography has been advocated as a diagnostic method when thromboembolic disease is suspected, although it is a very invasive method for unstable patients. However, the thermographic system can also describe the thrombus non-invasively by detecting areas of hypothe- mic region. For the medical treatment of thromboembolic diseases in humans with arterial thromboembolic disease, direct intra-arterial delivery of urokinase [14] and tissue plasminogen activator (t-PA) [7] are more effective in re- canalization than intravenous delivery. In the field of veter- inary medicine, successful thrombolysis by intra-arterial administration of urokinase was recently reported in a single case with arterial thromboembolism [9].

In this report, we describe the clinical and thermographic findings of arterial thrombosis (AT) and the local intra-arterial administration of streptokinase for the treatment of canine AT complicated by malignant mammary gland tumor (MGT).

An 8-year-old intact female Maltese dog presented for acute right hindlimb paralysis. On initial physical examination, unilateral posterior paralysis was observed, and the femoral pulse was weak. The affected limb was hypothermic. Concerning the history of the previous illness, the dog had several mammary gland lumpectomies because of recurrent malignant MGTs diagnosed histopathologically. At presentation, there was a newly formed MGT greater than 5 cm in diameter without evidence of metastases (Fig. 1A). A fine needle aspiration on the MGT demonstrated an increased ratio of the nucleus to the cytoplasm, prominent nucleoli, and anisokaryosis indicating mammary carcinoma (Fig. 1B). The histopathological examination of the MGT showed a mammary gland adenocarcinoma (stage III, T3N0M0). Blood work revealed elevated aspartate transaminase (AST, 84 U/l), alkaline phosphatase (ALP, 318 U/l), lactate dehydrogenase (LDH, 228 U/l), and creatine kinase (CK, 2000 U/l). The results of coagulation tests (D-dimer, 2.1 µg/ml; fibrin degradation products [FDP], 20 µg/ml) were markedly increased. Neurological examination revealed right hindlimb paralysis and knuckling with decreased muscle tone and postural reactions, as well as pronounced decreased deep pain (Fig. 1C).

Survey radiographs and orthopedic examination of the affected limb were unremarkable. Echocardiography findings were also unremarkable. On Doppler ultrasonography, arterial flow was not detected below the origin of the right deep femoral artery. The size of bilateral adrenal glands was within normal limit. Based on the history and results of physical, orthopedic, neurological, and histopathological examinations, and blood work, an AT was suspected as

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For the determination of the anatomic location of AT non-invasively, a thermographic study was performed. A thermogram obtained using an IRIS-5000 apparatus (Medicore, Kyungki, Korea) revealed infrared radiation below the origin of the right deep femoral artery and was markedly reduced from that of left hindlimb (Fig. 2A). For treatment, streptokinase (Kyungdong Parm, Seoul, Korea) was administered parenterally immediately after the diagnosis, for the purpose of thrombolysis. This agent (90,000 IU) was administered by intravenous infusion over 30 min and followed by a constant rate infusion of 45,000 IU per hour for 12 hr. The antithrombotic agent, heparin (Heparin sodium; Choonwae Pharma, Kyungki, Korea), was administered at 200 IU/kg by intravenous infusion, and then 100 IU/kg by subcutaneous injection per 6 hr. However, the general clinical symptoms remained unchanged with the right femoral pulse being non-palpable and the right hindlimb being weak. Therefore, the following day, we undertook local intra-arterial administration of streptokinase with thermography guidance. Arterial access via skin incision over an affected limb under sedation was carried out. The presence of thrombus in the right deep femoral artery was confirmed grossly (Fig. 3). A 22 G catheter (BD IV Catheter; Becton Dickinson Korea, Seoul, Korea) was introduced into the femoral artery and to the level of the thrombus. Streptokinase (250,000 IU/6 ml) was infused.
and aspirated repeatedly until dissolution of the existing thrombus. After three rounds of streptokinase infusion with an intervening time of 5 min, the patency of the right femoral artery was confirmed by a thermogram (Fig. 2B). The total duration of the procedure was 1 hr and the total amount of streptokinase administered into local intra-arterial was 125,000 IU. In our case, this local intra-arterial administration of streptokinase did not cause the severe hemorrhage or reperfusion syndrome including hyperkalemia and acidosis. Thereafter, antithrombotic medication with clopidogrel (Clopidogrel hydrogen sulphate; Jinyang Pharma, Seoul, Korea) was administered at 10 mg/kg, sid orally and a subsequent daily dose of 3 mg/kg was maintained for the prevention of re-thrombosis. As a result of this treatment, the right femoral pulse became palpable, and the patient regained almost normal gait and was discharged on the third post-operative day. The D-dimer and fibrin degradation products returned to normal 10 and 15 days after start of oral medication, respectively (Table 1) and profiles of serum chemistry reduced to normal range 12 days after the thrombolysis. To manage the malignant MGT, this dog had been administered carboplatin (carboplatin; Korea United Pharm, Choongnam, Korea) (10 mg/kg IV) for 10 months and clopidogrel (3 mg/kg PO q24 hr) was also administered. Ten months after presentation, the patient was still alive without occurring of re-thrombosis.

In both human and veterinary medicines, thrombi that form in vessel systems commonly cause marked morbidity and mortality. Distal AT characteristic results in peracute clinical signs of paralysis, pain, absence of pulse, and cold distal limbs [17], which are consistent with this case. A prospective study showed the frequency of platelet abnormalities was markedly increased in dogs with thromboembolic disease and neoplastic disease [13]. In addition, another recent retrospective study comprising 60 female dogs with mammary carcinoma showed more hemostatic test abnormality, of which the likelihood was increased in those with stages III and IV neoplasia [19]. In this case, since we ruled out any other causes of the hypercoagulability including heart disease and hyperadrenocorticism, an arterial thrombosis was highly suspected as a complication of the hypercoagulability from malignant mammary gland tumor. Therefore, it is important to consider AT as a differential diagnosis in canine cancer patient with an acute onset of pelvic limb neurological deficits. In diagnosing thromboembolic disease, traditional diagnostic methods (contrast angiography and nuclear scintigraphy) may be markedly invasive for the patient’s clinical condition. However, the thermographic system can be considered a simple and non-invasive method to diagnose the thromboembolism by detecting areas of hypothermic region. Decreased blood flow is evident as a hyporeactive nodule. In addition to the diagnosis of the AT, the thermographic device may be a promising monitoring tool of local-arterial thrombolysis. Early recognition of perfusion success is made intraoperatively [20]. Of the laboratory markers, D-dimer has shown clinical utility in the detection of early thromboembolism in human and dogs [3, 13]. In this case, the result of thermography was in good agreement with the hypothermic limb with AT and D-dimer was markedly increased. The present blood analyses revealed elevated ALT and AST as a result of hepatic and skeletal muscle inflammation and necrosis. LDH and CPK enzymes were greatly increased, consistent with widespread cellular injury [5, 18]. Medical treatment aimed at thromboembolic diseases consists of dissolving existing thrombi (thrombolytic drugs) or preventing new thrombus formation, primarily by means of the use of antiplatelet drugs, heparin products, and vitamin K antagonist. Streptokinase is the most common thrombolytic drug and causes thrombolysis by accelerating activation of fibrin-bound plasminogen to plasmin [10, 11]. Three meta-analyses compared the mortality and amputation rates in human patients with acute limb ischemia undergoing thrombolytic therapy or surgical vascular restoration. It showed better outcome in thrombolytic therapy than in surgery [15, 16, 22]. Although many other studies have also compared surgical thrombectomy with medical thromboly-

### Table 1. Profiles of D-dimer and FDPs after thrombolysis treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0(a)</th>
<th>Day 3(b)</th>
<th>Day 9</th>
<th>Day 13</th>
<th>Day 18</th>
<th>Day 35</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (µg/ml)</td>
<td>2.1</td>
<td>2.1</td>
<td>0.8</td>
<td>0.4</td>
<td>0.9</td>
<td>0.1</td>
<td>Below 0.5</td>
</tr>
<tr>
<td>FDPs(c) (µg/ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>Below 20</td>
</tr>
</tbody>
</table>

a) Day of first presentation.

b) Day after thrombolysis treatment and start of oral anticoagulants medication regimen (clopidogrel, 3 mg/kg PO q 24).

c) FDPs: fibrin degradation products.
sis in people, there is no clear-cut evidence supporting one intervention over the other in patients with AT. However, a recent study recommended that intra-arterial thrombolytic therapy rather than surgical embolectomy is performed in human patients in the acute (~14 days) phase of AT [4, 22]. Although successful thrombolysis by intra-arterial administration of thrombolytic agent was reported in human and feline arterial thromboembolic disease, it has not been reported in dogs [9, 14]. In this canine patient, thrombolysis with streptokinase by intra-arterial access was successfully curative than intravenous administration.

In our case, interestingly, systemic bleeding or hyperkalemia was not a clinically relevant problem after thrombolytic therapy with streptokinase. Streptokinase is a non-selective thrombolytic agent, which theoretically makes systemic bleeding complications more likely following intravenous administration of streptokinase compared with selective thrombolytic agents [7]. However, local intra-arterial infusion and aspiration method in this case is believed to allow better targeting of the fibrin (plasminogen) in the thrombus than systemic administration, and is assumed to be unlikely to induce a systemic fibrinolytic state much like previous report [9]. Additionally, the development of severe hyperkalemia following reperfusion is also a serious complication of thrombolytic therapy in dogs and cats with AT. Hyperkalemia likely results from reperfusion of necrotic tissue. Reperfusion injury leads to the release of high levels of potassium that are contained within cells [5, 10, 11, 17]. In our case, however, the partial AT localized to the unilateral femoral artery would induce limited ischemic cell damage. After thrombolysis, prophylactic management for thromboembolism in canine cancer patients is necessary. Clopidogrel is a newer antiplatelet drug that selectively inhibits adenosine diphosphate (ADP)-induced platelet aggregation and, thus, has a unique mechanism from the cyclooxygenase-inhibiting effect of aspirin [8, 10, 23]. The clinical effects and pharmacodynamics of clopidogrel have been evaluated in dogs and cats [6, 8, 12]. Recent study reported that clopidogrel therapy alone or in combination with ultralow-dose aspirin (ULDA) had similar antiplatelet effects compared with ULDA alone and was achieved without adverse effects in these species unable to tolerate aspirin therapy [12]. To minimize the potential gastrointestinal effects by ULDA treatment, we administered clopidogrel alone in this case. This patient has been well-controlled with oral clopidogrel and chemotherapy without recurrence of thrombosis for 10 months, after thrombolysis.

In conclusion, this case suggests that local intra-arterial thrombolysis with chemotherapy and oral clopidogrel might be a useful strategy for canine AT complicated by malignant mammary gland tumor. Furthermore, we suggest that the thermographic features of the thrombosis can help with the diagnosis and monitoring of canine AT, especially when contrast angiography is not easily available. Additional investigations are needed for confirmation and development of guidelines for the use of the thermography in dogs with thromboembolic disease.

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