Abstract

Background. Deep venous thrombosis (DVT) is one of the most prevalent medical problems today. On the contrary soft tissue sarcomas are rare tumors. The aim of the study is to analyze as the DVT or pulmonary embolism (EP) may be a pitfall in the early diagnosis of soft tissue sarcoma of the lower limb because both the rarity of these lesions and the imaging may not initially reveal a sarcoma as the cause for DVT.

Case Presentation. The authors report two clinical cases who presented a DVT and a EP. Physical examination and ultrasound didn't reveal a tumor but only the signs of DVT. Both were treated for DVT for several months. In view of persistent symptoms and inefficacy anticoagulant therapy, magnetic resonance imaging and biopsy were undertaken to uncover the underlying pathology.

Imaging and biopsy revealed a leiomyosarcoma, adherent to the femoral vein and to the femoral artery that were the cause of persistent symptoms despite anticoagulation, possibly by its local mass effect and also by its potential to create a thrombogenic milieu; Excision of the tumor followed by chemotherapy and radiotherapy, led to symptom regression.

Conclusion. Soft tissue sarcomas can present or mimic or be misdiagnosed with the DVT in particular in younger patients and in those with recurrent or refractory thrombosis or symptoms.. This two cases want to highlight the importance of considering neo-plastic masses as differential diagnosis in painful leg swelling. A delay of diagnosis and treatment of sarcoma may result in the poor prognosis.

Level of evidence. IV

Key words: soft tissue sarcoma, deep venous thrombosis, lower limb sarcoma, leiomyosarcoma, pulmonary embolism
Background

Sarcomas are relatively rare malignant tumors arising from the mesenchymal tissue, which consists of muscle, fat, bone, blood vessels, and fibrous and other supporting tissue. Sarcomas display a wide variety of histological subtypes and frequently involve the limbs (55% of cases), especially the lower extremities [1-3].

The incidence of soft tissue sarcomas (STSs) is approximately 15-35 cases per million person-years, accounting for less than 1% of all malignancies [1-3]. Around 3,200 new cases of STSs are diagnosed each year in the United Kingdom, while approximately 10,600 new cases were discovered in the United States in 2009 [4-5]. The incidence of STSs increases steadily with age and is slightly higher in males than in females. However, marked differences in age and sex distribution are seen depending on the histotype. For instance, rhabdomyosarcoma is more frequently observed in children and young adults, while synovial sarcomas typically affect young adult people. In contrast, malignant fibrous histiocytoma and liposarcoma generally occur in older adults [4-5].

Overall, the risk of thromboembolic events in patients with STSs is comparable with that observed in other orthopaedic conditions. However, STSs involving the hip or thigh have been associated with a particularly high risk of thromboembolism [6].

Deep venous thrombosis (DVT) and venous thromboembolism (VTE) are a common cause of morbidity and mortality in bedridden or hospitalized patients, as well as in generally healthy individuals. In the U.S., the incidence of DVT is approximately 80-100 cases per 100,000 person-years; the risk of DVT increases with advancing age, ranging from < 5 cases per 100,000 person-years in kids younger the 15 years to over 500 cases per 100,000 in persons aged 80+ years [7,8]. DVT is responsible for about 600,000 hospitalizations yearly in the U.S. The in-hospital case-fatality rate for VTE is 12% and rises up to 21% in elderly persons. The incidence of DVT is considerably higher in hospitalized patients compared with community-dwellings and varies from 20-70% [7,8].

Notably, the risk of thromboembolic events is much greater in cancer patients relative to the general population [9,10]. Indeed, patients with cancer are at 4- to 7-fold higher risk for VTE than those without cancer, with about 15% of cancer patients suffering at least a VTE episode. On the other hand, approximately 20% of patients presenting with VTE have an active cancer [11].

DVT is a rare, but not exceptional presentation of a STSs. Due to the remarkable difference in the incidence of the two conditions, this form of presentation is usually associated with a considerable delay in the diagnosis and treatment of the neoplasma. In the present study, we describe 2 cases of STS of the lower limb, the onset of which consisted of DVT and VTE. Because of the unusual presentation, in both cases diagnosis and treatment of the STS were significantly delayed. We also provide a review of the literature about the association between STSs and DVT.
Case Presentation

Two cases of soft tissue sarcoma of the lower limb with deep venous thrombosis and pulmonary embolism as initial presentation were observed in our Orthopaedic department. A 47-year-old man was diagnosed with an idiopathic DVT in the right distal femoral vein and the popliteal vein (Fig.1 A-B) and a 44-years-old woman with a massive pulmonary embolism (Fig.2 A). They were treated with therapeutic dose Enoxaparin respectively for 6 and 2 months; They did not have a prior history or family history of venous thromboembolic disease or miscarriages. Physical examination and ultrasound didn’t reveal a tumor but only the signs of deep venous thrombosis. In view of persistent symptoms and inefficacy anticoagulant therapy, they were referred to our orthopaedic institute and the magnetic resonance imaging and biopsy were undertaken to uncover the underlying pathology.

A PubMed search was performed using the terms “soft tissue sarcoma”, “deep venous thrombosis”, “lower limb sarcoma”.

In the first case (Fig.1 C-D) MRI showed a large tumor in the anterior muscle compartment of the right thigh, with an inhomogeneous appearance after administration of gadolinium, with multiple lymphadenopathy in the inguinal and external iliac region, with neoplastic thrombosis of the right common femoral vein with extension to the iliac veins ipsilateral common and inferior vena cava until to the confluence of the renal veins. We performed an excisional biopsy surgery. The tumor mass was found to be adherent to the femoral vein; Its section showed a neoplastic thrombus that obliterates the lumen to the common iliac vein. The biopsy showed a picture of high-grade leiomyosarcoma. Subsequently the patient underwent chemotherapy and radiotherapy. CT scan after 6 months shows multiple pulmonary metastases.

In the second case (Fig.2 B-C-D-E-F) MRI showed a large tumor in correspondence of the middle third of the right thigh, hypointense in T1 and T2 with enhancement after administration of gadolinium. The lesion is in close proximity to the artery that appeared deformed and to the superficial femoral vein that appeared compressed with signs of thrombosis. We performed an excisional biopsy, preceded by arterial embolization and followed by intraoperative brachytherapy. The tumor mass was found to be adherent to the superficial femoral vein. The biopsy showed a picture of high-grade leiomyosarcoma. After one year of follow-up the patient is asymptomatic and has no evidence of malignancy.
Conclusion

Literature review show only two case series and case reports about soft tissue sarcomas whose initial presentation is a DVT while there are not study in which is described as initial presentation an EP, except cases with a bone sarcoma [12-29].

Benns et al. reported that, out of 5234 patients treated for soft-tissue sarcomas, 19 patients had a medical history of both soft tissue sarcoma and DVT (0.36% of sarcoma patients); Among these patients 6 cases (0.11%) had DVT diagnosed before their soft tissue sarcoma; In these patients there were three cases with a malignant fibrous histiocytoma, one case with a leiomyosarcoma, one case with a pleomorphic sarcoma and the remaining case with a high-grade angiosarcoma. In 5 of these cases there was a delay in diagnosis ranging from one day to 12 months [14].

Arumilli et al report of three patients who presented with a painful swollen leg and were initially treated as a deep vein thrombosis or a baker's cyst, but later diagnosed as a pleomorphic sarcoma, a malignant giant cell tumor of the muscle and a myxoid liposarcoma [15].

Emori M showed two cases of soft-tissue sarcomas arising in the inguinal region may encompass or be adjacent to femoral vessels and result in venous obstruction, mimicking symptoms of DVT as swelling, pain, and discoloration in the affected extremities that were initially misdiagnosed as spontaneous DVT and administered unnecessary long-term anticoagulation therapy [16].

Many case report showed in four cases a leiomyosarcoma of the femoral vein, in two cases an arterial leiomyosarcoma involving the profunda femoris artery and the popliteal artery, a fibula Ewing sarcoma, malignant epithelioid angiosarcoma, a spindle cell sarcoma, a pelvic and a sacrum condrosarcoma and a liposarcoma, who developed a deep venous thrombosis of the lower extremity with initial misdiagnosis, delayed treatment, and a subsequently poor outcome [17-29].

Malignant neoplasm and its treatments as surgery and chemotherapy are risk factors for DVT; the eighteen percent of incident DVT cases can be attributed to active malignant neoplasm [30]. Concerning bone and soft tissue sarcoma, it was reported that 14.3% of 70 patients younger than 18 years of age with bone and soft-tissue sarcoma developed thromboembolic events [31], and 16% of children and young adults with sarcoma presented thromboembolic events [32]. Prandoni et al found malignancy in 3.3% of idiopathic DVT patients and in 17.1% of patients with recurrent DVT [33]; A similar study by Hettiarachchi et al found malignancy in 18% of patients presenting with DVT [34].

These reports indicate that DVTs in bone and soft-tissue sarcoma are frequent events, even compared with other cancer; in contrast Mitchell SY et al found that the risk of a clinically apparent thromboembolic event in patients with bone or
soft-tissue sarcomas is comparable with that in other orthopaedic patients. However, tumors in the hip or thigh may be associated with a particularly high risk of thromboembolism [35].

However, even if are common tumors that cause DVT, it’s unusual the presentation of those with DVT [23]. Our experience showed two cases of leiomyosarcoma confirming that this is the histotype more frequently associated with unexplained DVT in the literature. While soft tissue sarcomas account for 0.7% of all malignancies, leiomyosarcomas represent only 5% to 7% of soft tissue sarcomas, and only 2% of these are of vascular origin; This to testify the rarity of these lesions [16-22].

The tumor was the cause of persistent symptoms despite anticoagulation, possibly by its local mass effect and also by its potential to create a thrombogenic milieu; Excision of the tumor followed by chemiotherapy and radiotherapy in the first case and by brachitherapy and radiotherapy in the second case, led to a complete symptom regression in the second case at 1 years of follow-up and a partial regression in the first case.

A further cause of error may be due to the difficult differential diagnosis between a thrombus and a tumor by CT and MR imaging, because enhanced CT or MR imaging cannot raised easily distinguish a tumor thrombus from a blood clot, the inflammatory reaction environment may make complicate the diagnosis; an organized thrombus usually also shows low signal intensity on T1- and T2-weighted images, but the intensity may change, and this can sometimes confused the diagnosis [22].

Soft tissue sarcoma is a serious and potentially fatal neoplastic disease characterized by local extension and occasional distant metastasis that can present or mimick or be misdiagnosed with the deep venous thrombosis (DVT).

For these reasons, prompt diagnosis and appropriate management of soft tissue sarcoma is essential to minimize morbidity and mortality because a delay of diagnosis and treatment of sarcoma may result in the poor prognosis in tumor with survival rates if treated early ranged from 73% to 79% at 5 years [36-38]. This two cases want to highlight the importance of considering neo-plastic masses as differential in painful leg swelling.

In agreement with other authors with this article we want to focus the attention on this problem. All physicians should be aware that soft tissue sarcoma can present initially as DVT, particularly in younger patients aged <45 year without significant risk factors for DVT, and those with recurrent or refractory thrombosis or symptoms; in these patients a careful physical examination and ultrasonography in the inguinal region, MRI of the lower limb must be done to discover possible underlying malignancy because a delay in the diagnosis can be associate with a poor prognosis as happened in one of our case.
"Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal."

List of abbreviations

DVT: Deep venous thrombosis
EP: Pulmonary embolism
STSs: Soft tissue sarcomas
VTE: Venous thromboembolism

Competing interests: The authors declare that they have no conflict of interest.

Authors' contributions: All authors contributed equally to this work.
References


Figure legends

Fig. 1
Fig. 1 A,B: Doppler Ultrasonography shows neoplastic thrombosis of right femoral and iliac vein with arterio-venous micro fistulas.
Fig. 1 C,D: MRI of femur shows a leiomyosarcoma with neoplastic thrombosis of superficial and common femoral vein and of internal iliac vein.

Fig. 2
Fig. 2 A: TC scan shows pulmonary embolism
Fig. 2 B: Doppler Ultrasonography shows hypervascularization of the MFH
Fig. 2 C: Arteriography shows as the lesion is adjacent to the superficial femoral artery and vein
Fig. 2 D,E,F: MRI of left femur shows an MFH close to the superficial femoral vein and artery that are compressed and deformed

Table

Table 1: Publications on soft tissue sarcomas of the lower limb associated with deep venous thrombosis from PubMed ordered according to the number of cases described
Additional files provided with this submission:

Additional file 1: Table 1.doc, 40K
http://www.biomedcentral.com/imedia/2350008580406602/supp1.doc