Angiosarcoma of the lower limb misdiagnosed as deep thrombophlebitis – a review

Angiosarcoma do membro inferior simulando tromboflebite profunda – uma revisão

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Abstract

Angiosarcomas are very rare sarcomas with vascular differentiation, high-grade malignant behaviour, early metastasis and generally bad prognosis. Early diagnosis is very important for adequate radical ablative surgery in order to obtain a better prognosis. The authors present a case of very aggressive angiosarcoma of the leg, admitted in a very advanced stage with extensive metastases, due to an initial misdiagnosis of deep venous thrombosis. The patient died early during the period of evaluation. A review of superficial types of angiosarcomas is presented, including the clinico-pathological classification, characterizing its multifocal aspects, frequent extensive metastases, diagnostic studies for defining vascular tumours, early local recurrences after apparent radical ablative surgery, and therapeutic modalities.

Key Words: Angiosarcoma of the lower limb, Deep Thrombophlebitis, Lymphoedema

Resumo

Os angiossarcomas são sarcomas com diferenciação vascular, muito raros, de elevado grau de malignidade. Metastizam precocemente e têm, geralmente, mau prognóstico. O diagnóstico precoce é importante, de forma a proporcionar cirurgia ablativa radical, a qual poderá, eventualmente, melhorar o prognóstico. Os autores apresentam um caso de angiossarcoma da perna de comportamento muito agressivo, inicialmente diagnosticado como tromboflebite profunda. A doente foi admitida em fase avançada de doença, com múltiplas metástases, tendo "exitus" rápido durante a fase de estudo da situação. Os autores fazem uma revisão dos angiossarcomas superficiais, incluindo a sua classificação histopatológica, o seu aspecto multifocal, a precocidade de aparecimento de metástases em vários locais, estudos diagnósticos necessários para a caracterização de tumores vasculares, recorrências precoces após aparente cirurgia ablativa radical, e opções terapêuticas existentes.

Palavras chave: Angiossarcoma do membro inferior, Tromboflebite profunda, Linfedema

Introduction

Sarcomas are rare malignant tumors of mesenchymal origin, comprising approximately 1% of all cancers.[1] Angiosarcomas (AS) are malignant vascular sarcomas that comprise approximately 2% of all soft tissue sarcomas.[2] AS reproduce many of the functional and morphological features of normal endothelium. Their cytology varies between minimal atypia in well differentiated tumors hemangioma-like and markedly atypical tumors, which makes them difficult to distinguish from carcinomas or melanomas.[3] Contrariwise to old references, today it is assumed that it is not possible to define if AS display lymphatic or vascular differentiation, even in cases of AS arising in the setting of lymphoedema, that were previously called lymphosarcomas. Nowadays, in a recent update, the nosologic entity AS refers to all tumors showing endothelial differentiation regardless of whether the

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lesion is believed to be related to vascular or lymphatic endothelium[3]. Nevertheless some authors believe that in the future molecular and immunophenotypic methods may in time result in refinements of the classification of AS.[4] Many AS however have a mixed phenotype.[5]

Although AS may occur at any location in the body, they rarely arise from major vessels, their predilection being the skin and superficial soft tissue, in sharp contrast with the deep location of most soft tissue sarcomas. Generally one-third of AS occurs in the skin and about one-fourth in soft tissues, and the remainder at internal organs (e.g. heart, liver, bone, spleen).[6] Although Meis-Kindblom[7] in a series of eighty cases of AS refers to a higher percentage of cases in the limbs (40%), other series refers to the head and neck as the most frequent anatomical sites involved.[2,3,8]

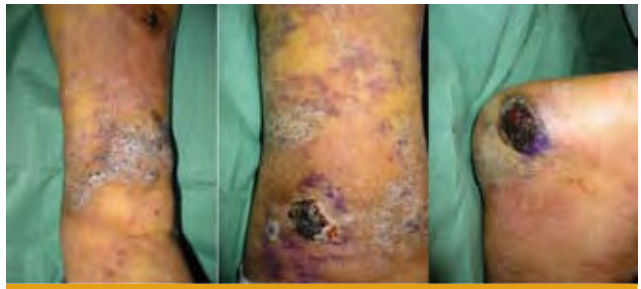
AS shows marked biological heterogeneity at different anatomic sites, regarding gender ratio, median age at diagnosis, and response to chemotherapy. Overall 5-year survival of about 31% in the case of AS with only superficial depth and negative microscopic surgical margins contrasting with a much worse prognosis in unresectable AS.[8] AS are collectively one of the rarest soft tissue neoplasias and are generally high-grade aggressive tumors that tend to recur locally and metastasize early despite aggressive multimodality therapy. The frequent local recurrence is due to the fact that lesions tend to be often more locally invasive than anticipated after adequate supposed resection. In addition AS behave often as multifocal lesions, whether or not this is clinically evident[9]. Sites affected by metastasis depend of the location of the primary tumor, but most commonly involve lymph nodes, lungs, liver, spleen and bone.

The authors present a case of very aggressive AS of the leg, misdiagnosed initially as deep thrombophlebitis, that was impossible to characterize in its initial location due to the fact that the patient appeared to us on a very advanced stage of evolution of the disease, but we thought that it could be assumed to be an initial deep subcutaneous type of AS, due to the fact the patient presented initially without lymphoedema nor superficial cutaneous lesions.

Case Report

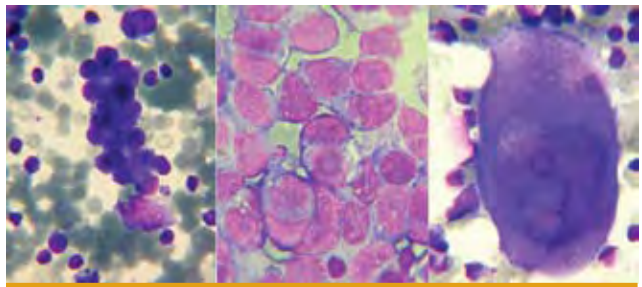
On August 12-2006 a 72-year-old white woman was admitted with a long-standing history of 8 months duration edema of left lower limb, that had rapidly begun on the leg and slowly progressing to the thigh. The situation was previously diagnosed as "erysipela" and the patient was treated with flucloxacilin, but without improvement. She was then consulted for two times by the same vascular surgeon in another hospital, who made a diagnosis of deep thrombophlebitis of the leg and prescribed a non-steroidal anti-inflammatory drug and subcutaneous low-molecular weight heparin that the patient did for 37 days, without success. One month before admission she noticed the appearance of several enlarging cutaneous erythematous violaceous nodules on the left foot and leg. Several lymphadenopathies of the left groin region were also palpable at that time. Fifteen days before admission the patient noticed several echymosis on the arms, legs, trunk and abdomen. The heparin was stopped two days before admission, when she suffered two episodes of slight hemoptysis. The family history was unremarkable and personal history only revealed a long duration of well controlled hypertension and hypercholesterolemia. At admission, the physical examination revealed pallor, without jaundice or cyanosis. The vitals were 120/60 mmHg blood pressure, 80 bpm heart rate, 24 cpm respiratory rate. The left malar region was slightly edematous. Heart and lung auscultation were normal. The liver was moderately enlarged and with firm consistency. No splenomegaly was detected.. Enlarged and firmly matted lymphadenopathies were found on the left iliac and inguinal regions. The lower left limb was frankly enlarged due to lymphoedema, mostly marked on the left foot and leg, where there were several erythematous violaceous hard nodules, the larger one ulcerated on the lateral border of the foot *(Figs 1 A,B,C)*. Blood tests revealed: Hb 9.5 g/dL; MCV 87 μm^3; MCHC 33.5 g/dL; reticulocytes 145.8X10^9/L (20.0-100.0); leukocytes 8.9^3/mm^3 (4.0-10.0) with neutrophils 62.2%, lymphocytes 22.7%, eosinophils 6.2%, monocytes 8.6%; platelets 59x10^9/L (150.0-400.0); ESR 39 mm (1st hour); I.N.R. 1.16 (0.86-1.20); APTT 24.3" (24.5-35.2); fibrinogen 595.9 mg/dL (175-400); ATIII 63.4% (80-120); serum vitamin B12 > 1000 pg/mL (239.0-931.0); D-dimers 529.5 ng/mL (< 300); negative Coomb's tests; LDH 842 U/L (313-618); albumin 3.68 g/dL (3.50-5.00); normal protein electrophoresis. Other blood tests were normal: sideremia, transferrin, ferritin, folic acid, protein C, protein S, factor V; AST/ALT, ionogram, calcium, phosphate, magnesium,

glucose, creatinine, BUN, CPK. Lupus anticoagulant, platelet antibodies and Coombs tests were negative. Urinary sediment was normal. HBV; HCV and HIV serology were negative. Electrocardiogram was normal. Thorax x-Ray disclosed bilateral moderate pleural effusion. We proceed to several CT scans, with the following abnormalities: a) neck (normal); b) thorax (bilateral pleural effusion, small areas of bilateral passive atelectasia of the lower lobes of the lungs, infracentimeter nodular area on the periphery of upper right lobe, lymphadenopathies of the right hilar region and of the mediastinum in pre-tracheal retrocava topography measuring the largest one 15mm in greatest axis); c) abdomen (micronodularity of the small epiplon with one centimetric lymphadenopathy); d) pelvis (lymphadenopathies of the left iliac regions and also of the homolateral inguinal region, the larger ones with transversal diameters of 15 and 20 mm). We observed a rapid clinical and laboratorial deterioration with development of pneumonia of the left lung and left heart failure, hypertensive crisis on the 10^{th} day of admission with BP 20.5/10.8 cm Hg, tachycardia, diaphoresis, polypnea, and bilateral diffuse wheezing and terminal inspiratory medium crackles. There were also worsening of several blood tests, which at 10 days after admission revealed: Hb 6.4 g/dL; MCV 88 μm^3, MCHC 29.1g/dL; leukocytes $20.7^3/mm^3$ (neutrophils 54.7%, lymphocytes 36.7%, eosinophils 2.2%, monocytes 6.1%), platelets $22.x10^9$/L; I.N.R. 1.29; APTT 19.8"; fibrinogen 385.7 mg/dL; LDH 1310 U/L; albumin 2.9 g/dL. Medullary blood immunophenotypage was negative for monoclonal lymphocytic population, but myelogram disclosed extensive infiltration of the bone marrow by cells with variable medium and high-grade size, pleomorphic, some with ill-defined cellular limits and frequently arranged in nests, with hyperbasophilic and vacuolized cytoplasma, high nuclear/cytoplasma ratio, loose chromatin and ill-defined nucleolus, some with multilobulated nucleus, and rare images of emperipoilesis *(Figs 2 A,B,C)*. Not sufficient material on bone biopsy was obtained for an adequate interpretation, but areas of sparse hematopoietic tissue revealed individualized paratrabecular pleomorphic cells with lumpy chromatin and nucleolus. Skin biopsy revealed infiltration of the skin and dermis by malignant neoplasia, characterized by vascular spaces lined by atypical endothelial cells with very pleomorphic and irregular nucleus, prominent nucleolus and voluminous eosinophilic cytoplasm *(Figs. 3 A,B,C,D,E,F)*. In several areas the tumor assumed an epithelioid architecture. Immunohistochemistry study was positive for CD31 marker *(Figs. 3 G,H), ulex europaeus* and focally for factor VIII, and negative for HMB45, AE1/AE3, LCA and protein S100. Her family denied necropsy, but an immediate post-mortem study of a lymph node of the left groin showed rich cellularity, characterized by isolated cells or nests of cells of variable volume and cohesion, with accentuated nuclear polymorphism and coarse chromatin, cytoplasm sometimes elongated or polyedric, and some stroma in between the nests of cells. Despite large spectrum antibiotherapy, heart failure therapy and red cell transfusion, the patient died 10 days after admission during the study of its clinical situation. No cytogenetic studies were done because they are not available in our hospital.



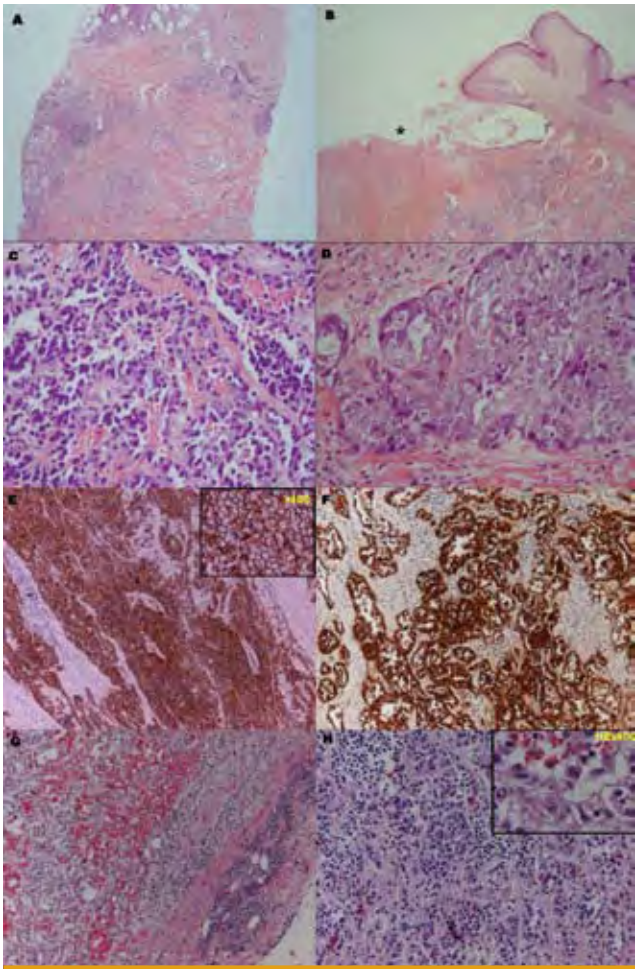
A/B – Multiple violaceous papules and marked lymphoedema; C – Large ulcerated tumor of the foot with easy bleeding.

FIG. 1



Bone marrow aspirate: MGG10x100: A - Tight clumps of malignant cells; B – Malignant cells with high nucleocytoplasmic ratio, diffuse chromatin pattern and moderated abundant basophilic cytoplasm with some vacuoles; C – Emperilopoiesis (pseudophagocytosis): a megacariocyte engulfed a granulocyte.

FIG. 2



A – HEx40: Infiltration of the dermis by malignant neoplasia; B – HEx40: Malignant infiltration of the dermis with papillary hyperplasia of the epidermis and ulceration*; C – HEx250: Vascular channels lined by atypical cells; D – HEx400: Malignant neoplasia with epithelioid pattern and marked cellular pleomorphism; E – Immunohistochemistry of skin biopsy – CD31x100; F – Immunohistochemistry of skin biopsy positive with *ulex europaeus*; G – HEx100: Metastasis in an inguinal lymph node; H – HEx250: Metastasis in an inguinal lymph node.

FIG. 3

Discussion

According to Weiss,[3] superficial AS can be subdivided in: a) cutaneous AS of the usual type unassociated with lymphoedema; b) cutaneous AS associated with lymphoedema; c) AS of deep soft tissue. Although the ethiopathogenesis of AS is generally unknown, some cases occur in association with previous radiotherapy,[10] in areas adjacent to foreign material,[11] in the vicinity of arteriovenous fistulas in renal transplant patients,[12] in association with some genetic syndromes (e.g. Kilppel-Trénaunay syndrome, Maffucci syndrome), or with other tumors.[13] Environmental carcinogens are involved in the pathogenesis of some AS, as in the case of liver AS due to use of thorium dioxide (Thorotrast) in angiography,[14] vineyard workers exposed to AsO_3-containing insecticide or industrial workers expose to vinyl chloride during the production of synthetic rubber.[3]

Cutaneous AS of the usual type unassociated with lymphoedema is the most common type of superficial AS. It primarily affects the elderly persons and is usually located on the head and neck, clinically presenting as macular or nodular purple lesions with poor defined haemorrhagic margins, sometimes initially appearing bruises or hemangiomas, delaying the diagnosis and causing the patients coming to Hospital at advancing stage.[15] Nodular elevated lesions sometimes ulcerate. The tumors extensively involve the dermis and more deep structures, such as subcutis and fascia, which may be involved by the rapidly growing tumors.

AS associated with lymphoedema or Stewart-Trèves syndrome are usually secondary to radical mastectomy and lymph node dissection for breast carcinoma, causing chronic lymphoedema.[16,17] They are rarely found in the abdominal wall, following lymph node dissection for carcinoma of the penis and chronic lymphoedema secondary to obesity,[18] or on the arm or leg affected by congenital, idiopathic[19] or traumatic lymphoedema, in chronic lymphoedema associated with immobility,[20] and in lymphoedema associated with filarial infestation.[21] AS generally occurs only many years after the beginning of lymphoedema,[22] and is characterized by one or more polymorphic lesions in a brown non-pitting edema of the affected skin. Some of the lesions, located in the subcutis, impart a mottled purple red hue to the skin, whereas the superficial nodular or polypoid lesions can ulcerate.[3]

AS of deep soft tissue, are the less common of the AS. They usually are restricted to deep soft tissue, occurring at any age. About one-third develop in association with other conditions such as inherited diseases (Neurofibromatosis, Klippel-Trénaunay and Maffucci syndromes – the association of multiple enchondromas and cutaneous hemangiomas),[23] synthetic vascular grafts, and other neoplasias. These AS tend to occur on the extremities or in the abdominal cavity,[24] where it could present as a large and

hemorrhagic mass. Sometimes they can masquerade as a chronic hematoma. In very young patients the large size of the tumor may result in hematologic abnormalities such as thrombocytopenia, high-output cardiac failure from arteriovenous shunting, or even death due to massive exsanguination.

AS occasionally arises in deep intramuscular soft tissue of a limb or limb girdle, they can be initially mislead as deep venous thrombosis, due to edema and early invasion of nearby structures. They quickly develop metastasis.[25] The possibility of an underlying neoplastic pathology shall be considered whenever there is no response to anticoagulant therapy and if occurs compromise of overlying skin. Despite extensive bibliographic search no references were found by us, to the association of thrombophlebitis of the legs with angiosarcoma of the legs, although there are references of thrombophlebitis on angiosarcoma with other locations.

The histopathological features of AS are diverse. We may find both spindle and epithelioid areas, arranged in sheets, nests, cords and rudimentary vascular channels with an infiltrative pattern of growth. The diagnosis can be suspected in light microscopy, when the vascular structures are apparent. The neoplastic vascular channels have an irregular morphology, randomly anastomosing in a sinusoidal fashion. The vascular channels can be lined by a single layer of neoplastic endothelium, with little atypical features, resembling hemangioma. In the less differentiated cases there are endoluminal proliferation, papillae and solid areas. Sometimes the tumor cells have a more rounded and large shape, abundant eosinophilic or amphophilic cytoplasm with vesicular nuclei. This epithelioid variant can be misleading with carcinoma and melanoma.[3]

The immunohistochemistry is a powerful tool in the diagnosis of the poor differentiated forms of angiosarcoma. As a vascular tumor, they express vascular antigens, like Factor VIII or von Willebrand factor, CD31 (platelet–endothelial cell adhesion molecule), CD34 (human hematopoietic progenitor cell antigen) and the *ulex europaeus*. Cytoqueratin markers are present in one third of the tumors, particularly, the epithelioid forms. The CD31 marker combines both a relative specificity with a good sensibility (90% positivity in all forms of angiosarcoma). Factor VIII is one of the most specific markers for vascular tumors, but lacks sensitivity, being present as a weak focal staining in a minority of angiosarcomas.[3]

Electron microscopy is useful in the equivocal cases; the finding of a specific tubular structure, the Weibel-Palade bodies can identify the most undifferentiated tumors.[26]

Cytogenetic studies of soft tissue AS are scant and limited to isolated cases. Almost all reported AS karyotypes have shown complex aberrations. No consistent chromosomal abnormality has yet benn identified. However, some cytogenetic changes reported in tumors from different locations revealed similarities. Among the most common changes were gains of 5pter-p11, 8p12-qter, 20pter-q12 and losses of 4p, 7p15-pter, -Y and abnormalities involving 22q. Flow cytometric studies have shown diploid, tetraploid and aneuploid patterns. No significant correlation between clinical outcome and DNA ploidy pattern has been reported.[25]

There are just a few reports on radiological findings of AS with lymphoedema. CT scan reveals extreme skin thickening, multiple cutaneous nodules, marked increase in the attenuation of subcutaneous fat, and collection of fluid within muscles and surrounding tissue. MRI generally shows hypo-intensity on T1-weighted images and hypo or hyper-intensity on T2-weighted images, besides heterogenous enhancement following intravenous administration of gadolinium.[26] The different signal intensity on T2-weighted images may reflect the proportion of vascular spaces to tumor cells and fibrous stroma. Dynamic MRI may strengthen the statements about abundant neovascularity throughout the tumors.[27]

Wide surgical resection or amputation has been advocated as the treatment of choice in adult AS, with radiotherapy reserved for symptomatic relief in operable cases. Although the biological behavior is unpredictable some AS undoubtedly respond to either chemotherapy or radiotherapy if early treatment is possible. Prognostic data for adult cutaneous AS after surgical removal depends in greater extent on the characteristics already referred of these tumors. For Cooper[28] local recurrence is seen in 80% and metastasis in 50% of cases, resulting in a median survival of 20 months and 5-year survival of 15%, while Maddox[29] refers to series with survivals between 10 and 35%.

Chemotherapy also is not able to obtain good results, although some agents like paclitaxel, doxorubicin and pegylated liposomal doxorubicin,[8] can

sometimes achieve a partial and temporary improvement with progression free survival of several months. Exploration of purportedly anti-angiogenic "metronomic" chemotherapy dosing (i.e., low-dose weekly taxanes in combination with newer anti-angiogenic or other cytotoxic agents) are in an experimental phase.[30] New approaches not yet tested, such as targeting of vascular endothelial growth factor pathways using agents such as bevacizumab, SU11248, and BAY43-9006, alone or in association with standard cytotoxic agents, are an interesting line of investigational therapy.[30]

Our patient was admitted in a very advanced stage of disease, without any possibility to obtain amelioration, with death in a precocious phase of investigation. The initial clinical manifestation simulating a picture of deep thrombophlebitis of the leg was responsible for the late diagnosis. We cannot consider that this patient had a case of Stewart-Trèves syndrome, because the lymphoedema occurred after the initial clinical manifestation of the disease and the evolution was very short. It is possible that the patient had a deep subcutaneous type of AS, with very aggressive behavior due to its undifferentiated histopathology. ■

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