Angiosarcoma arising in sclerodermatous skin

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SUMMARY

We report a case of cutaneous angiosarcoma in a 77-year-old female patient with systemic sclerosis. The tumor developed around a large telangiectasia in the left temporal region. Later on, extensive asymptomatic redness and edema with several nodules over the whole left side of the face developed. Since the conservative therapy failed to produce any improvement, a diagnostic skin biopsy was performed. The pathohistological diagnosis was moderately differentiated angiosarcoma. The patient was treated with a combination of chemotherapy and electron beam irradiation. Despite a notable cutaneous improvement, the control check-up revealed the presence of metastases of the lung and liver. This is the first report of cutaneous angiosarcoma occurring in sclerodermatous skin. The possible pathogenesis of this rare tumorogenic transformation of soft tissues is discussed.

Introduction

Transformations of benign vascular malformations in malignant lesions have been recently reported, representing an unusual event in soft tissue tumorogenesis. There are only a few case reports in medical literature of angiosarcoma spontaneously arising in hemangioma or in a vascular malformation (1). Until today, angiosarcomas have been described as arising in pre-existing benign vascular tumors, including lymphangioma and "port wine-stains", and in benign and malignant nerve sheath tumors (2–4). They have also occurred as a complication of varicose ulceration, arteriovenous fistulae, renal transplantation, hereditary epidermolysis bullosa, xeroderma pigmentosum, a gouty tophus, retained foreign materials such as shrapnel and surgical sponges, and adjacent to a dacron vascular prosthesis (5–11). Human herpesvirus type 8 has been detected in several cases, but excluded in others (6, 12, 13). Intravascular dissemination of an angiosarcoma mimicking angioendotheliomatosis has been described (14).

No case of sclerodermic telangiectasia transforming into angiosarcoma has been reported. We believe that immunological disturbance in systemic sclerosis and therapeutically induced immunosupression were poten-

KEY WORDS

angiosarcoma, systemic sclerosis, telangiectasia
Case report

A 77-year-old woman with an 8-year history of systemic sclerosis came to our Outpatient department because of an erythematous, firm edema encompassing the entire left side of the forehead, nose, face and...
Histochimically the tumor cells were vimentin, with erythrocytes were observed (Figure 3). Mitotic activity and occasionally vascular lumina filled nuclei. Neoplastic cells crossed collagen bundles forming cuboidal endothelial cells, with large hyperchromatic nuclei, anastomosing vascular channels lined with atypical, differentiated angiosarcoma.

Partially excision of the small nodular lesion from left temporal region was performed. The histological slides were stained with hematoxylin and eosin with additional immunostains for cytokeratin, vimentin, factor VIII, CD31, Ulex europaeus agglutinin, and S-100 (all Dako, Denmark) using a standard avidin-biotin-peroxidase complex procedure.

Microscopic examination revealed a well-to-modera
tely differentiated tumor tissue composed of irregular, Anastomozing vascular channels lined with atypical, cuboidal endothelial cells, with large hyperchromatic nuclei. Neoplastic cells crossed collagen bundles forming irregular anastomosing channels. Some of the cells contained vacuoles within their cytoplasm (Figure 2). Mitotic activity and occasionally vascular lumina filled with erythrocytes were observed (Figure 3). Immunohistochemically the tumor cells were vimentin, Ulex europaeus agglutinin, factor VIII and CD31 positive. Cytokeratin and S-100 immunostains were negative. The pathohistological diagnosis was a moderately differentiated angiosarcoma.

Laboratory examination revealed an elevated sedimentation rate, syderopenic anemia with an elevated incidence of γ-globulins. The patient’s serum ANA was positive (1:160), and both the scl-70 antibodies and the anticiardiolipin antibodies were positive. Esophageal-gastroscopic examination revealed reflux esophagitis of the first grade. Pulmonary function showed abnormal vital capacity and a low diffusing capacity. The abdominal ultrasound was within normal limits.

Because of the progressive centrifugal infiltration of the skin on the right face, radiotherapy was not appro-
priate. According to the oncological protocols, a treatment of 10 cycles of chemotherapy with epirubicin (100 mg every three weeks) was instituted. After the eighth cycle the cutaneous lesions regressed partially (Figure 4). Symptoms of systemic scleroderma, such as restricted opening of the mouth and inability to straighten the fingers receded in the opinion of the patient. At that time a skin necrosis in the left cubital region appeared due to a paravenous drug application. After cessation of therapy, the tumor on the face continued to grow rapidly. It was decided to continue with electron beam irradiation using fractionated doses of 2 Gy five times per week up to a total 50 Gy. At the end of the treatment a remarkable regression of cutaneous lesions was noted, but metastases of the lung and liver were detected on control chest x-ray and abdominal ultrasound examination.

Discussion

The vasculature and, in particular, the endothelial cells are the primary involved structures in the pathogenesis of systemic sclerosis (16). Serum of these patients is directly cytotoxic to endothelial cells and via antibody-dependent cellular cytotoxicity. The influence of serum from affected patients on in vitro angiogenesis varies with the phase and type of disease. It is stimulatory in early limited disease, but in chronic diffuse disease becomes inhibitory (17). The fibromucinous changes in the vascular endothelium appear to be the primary pathology. Damaged endothelium causes vascular occlusion and tissue ischaemia occurs. In vivo markers of platelet activation are increased. Levels of fibrinogen, von Willebrand-factor antigen and other plasma proteins are raised and contribute to increased plasma viscosity, further reducing microvascular blood flow (18). Anticardiolipin antibodies are present in more severely affected subjects and may cause endothelial cell damage (16). There is also an excessive response of fibroblasts to transforming growth factor-β (TGF-β), platelet derived growth factor (PDGF), and to serum from patients with this disorder (19). All the above-mentioned observations suggest that a microvascular injury with subsequent fibrosis is present early in the course of systemic sclerosis.

Angiosarcoma is a rare aggressive malignancy first identified as a distinct clinical entity by Wilson Jones in 1964 (20). The term angiosarcoma includes several closely related entities, with different presentations and behavior. It is most commonly present in three different clinical settings: idiopathic cutaneous angiosarcoma of the head and neck, angiosarcoma complicating lymphedema, and post-irradiation angiosarcoma. A miscellaneous category is sometimes added (21). Approximately 50% of angiosarcomas are found on the face and scalp of elderly patients, with predominance among
cases is unknown. Neither such a case nor any mechanism of transformation from telangiectasia to that it had developed from a vascular dilatation. The clinical history and location of the tumor suggested itable erythema and an edema with nodules developed. Around one telangiectasis remarked as a characteristic sign. Histologically cutaneous angiosarcomas are usually well-to-moderately differentiated lesions, composed of irregular vascular channels lined by atypical, plump, hyperchromatic endothelial cells. In a small number of cases this form of angiosarcoma is presented as a high-grade, highly pleomorphic tumor with rudimentary lumen formation, which can be difficult to distinguish from carcinomas and high-grade sarcomas. In such case immunohistochemical analysis using endothelial specific antibodies like Ulex europaeus agglutinin, antibody to factor VIII related and CD 31 and 34 antigens, as well as ultrastructural analysis usually help to confirm the diagnosis (21, 30, 31). Sometimes is difficult to delineate low-grade angiosarcoma from early vascular lesion of Kaposi’s sarcoma. The vessels in Kaposi’s sarcoma are usually more irregular, and in low-grade angiosarcoma there is usually some evidence of cellular atypia. Also, small intravascular endothelial buds, irregular jagged vessels, dissection of collagen bundles by vascular structures, and inflammatory cell infiltrates are also to be observed (21).

After eight cycles of chemotherapy excellent results were observed in our patient. Unfortunately a paravenous application produced severe complications which necessitated cessation of cyotoxic therapy. After induction of electron beam irradiation therapy a further regression was observed in the tumor, but lung and liver metastases were found in the course of control scans.

We observed many telangiectases on the face which is a characteristic sign. Around one telangiectasis remarkable erythema and an edema with nodules developed. The clinical history and location of the tumor suggested that it had developed from a vascular dilatation. The mechanism of transformation from telangiectasia to angiosarcoma is unknown. Neither such a case nor any coincidental appearance of scleroderma and angiosarcoma has been reported in medical literature to our knowledge. The immunocompromised status due to systemic sclerosis and periodical corticosteroid and cytotoxic therapy could be contributory factors to the malignant alteration. Probably, a similar pathogenetic mechanism could be responsible for the appearance of angiosarcoma in arteriovenous fistula for dialysis in the case of an immunosuppressed renal transplant recipient, as reported by Bessis (26).

There are only few case reports in the literature of angiosarcoma spontaneously arising in a hemangiomia or in a vascular malformation (1). In 1970 Girard et al. described three cases of low grade angiosarcoma arising in port-wine stains on the backs of three children (3). Rossi et al. recently reported four cases of deep-seated soft tissue angiosarcoma arising in hemangiomia (vascular malformation) with well-documented benign and malignant histological features (1). In 2001 Yamamoto et al. reported angiosarcomatous transformation in skeletal hemangiomatosis in a patient who had been exposed to atomic bomb irradiation, after more than 50 years (32).

We did not find the presumed benign telangietectasia component in our histological slides, as Rossi (1) et al. had described it in their report, probably because our biopsy specimen was relatively small. The scleroderma skin was very smooth, hard and in a critical anatomical location which prevented the total excision of the suspected lesion.

It is interesting that recent experimental studies on pathogenesis of angiosarcoma support the possibility that malignant transformation occurs in benign endothelial cells. This is characterized by over-expression of vascular endothelial growth factor (VEGF) in the presence of p53 mutation. Namely, dysfunction of the p53 seems to occur as an early event in the pathogenesis of vascular disorders, malformations and development of angiosarcoma, whereas over-expression of VEGF could play an important role in the progression of angiosarcoma (33).

The impaired immunological situation in a systemic sclerosis in the presence of many large telangiectases, low-dose immunosuppressive therapy, and immunologic factors acting on endothelial cells could all be inducers of malignant transformation in our patient. Further investigations are necessary to elucidate the exact mechanisms of this rare transformation in soft tissue tumorigenesis.

REFERENCES


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