

## Case Report

# An elderly woman presented with an aggressive hemifacial mass: a case of angiosarcoma

## 一名年老婦人半邊面頰有急遽增生的腫塊：血管肉瘤一例

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A 78-year-old lady presented with an aggressive rapidly-growing right facial infiltrative mass and neck lymph node. Pulmonary and skeletal involvement were also identified. The diagnosis of metastatic angiosarcoma was made. Clinical features, risk factors, histological features and various treatment modalities (surgery, adjuvant radiotherapy, vascular targeted therapy) of angiosarcoma will be discussed.

一名七十八歲女仕因右邊面部有急遽增大的厚實腫塊及頸部淋巴結而求診。因檢查時發現已有肺部及骨骼的轉移，其診斷為轉移性血管肉瘤。本文將討論此病的臨床特徵、風險因子、組織學特徵及各種治療方法。

**Keywords:** Metastatic angiosarcoma

**關鍵詞：**轉移性血管肉瘤

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## Introduction

Angiosarcoma is a rare aggressive soft tissue sarcoma of endothelial cell origin with a poor

prognosis. It usually affects the head, neck or scalp in the elderly. Surgery with adjuvant radiotherapy remains the main treatment option. The development of vascular targeted therapies provides a potential treatment for angiosarcoma.

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## Case report

A 78-year-old lady with good past health presented with an asymptomatic right hemifacial non-itchy infiltrative erythematous mass for one month (Figure 1). There was a rapid progression of the eruption which subsequently involved the whole right hemi-face and the right submandibular region (Figure 2). One firm, non-tender, 2 cm supraclavicular lymph node was



**Figure 1.** An elderly woman presented with an infiltrative right hemi-facial erythematous mass.

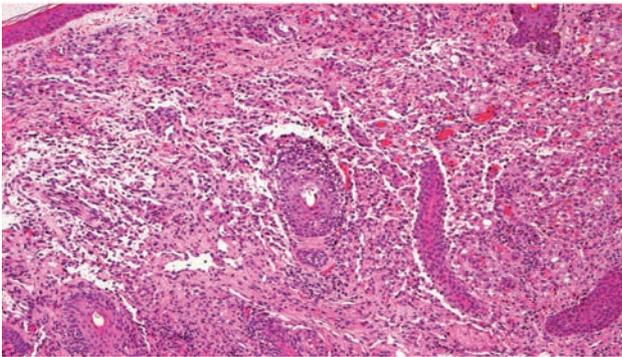


**Figure 2.** Right submandibular mass.

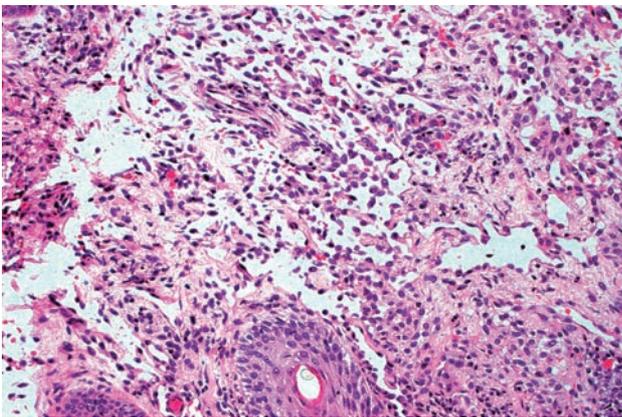
palpable. The complete blood picture, renal function tests, liver function tests and creatine kinase were all normal. The anti-nuclear antibody was 1:640 while the anti-double-stranded DNA and anti-extractable nuclear antigen antibodies were both negative. X-ray sinus showed no evidence of sinusitis. Differential diagnoses included facial cellulitis, erysipelas, mycobacterial infections (lupus vulgaris, leprosy), lupus erythematosus tumidus, acute cutaneous lupus erythematosus, dermatomyositis, angiosarcoma, folliculotropic mycosis fungoides, granuloma faciale, lymphocytic infiltrate of Jessner and granulomatous rosacea. She was prescribed a 2-week course of ampicillin and cloxacillin but there was no improvement.

An incisional skin biopsy over her right chin was performed. The skin biopsy showed an infiltrative vascular tumour throughout the dermis (Figure 3). The tumour was composed of irregular branching vascular channels lined by plump spindle to oval endothelial cells with mild nuclear atypia (Figure 4). Aggregates of epithelioid cells with occasional cytoplasmic vacuoles were seen (Figure 5). Mitosis was rare. Immunohistochemical study revealed CD34 positive epithelioid cells. Therefore, the histological diagnosis of angiosarcoma was made. Left supra-clavicular lymph node fine needle aspiration cytology was performed which revealed scattered, large size, highly pleomorphic epithelioid malignant cells with positive staining for CD31 and CD34. A positron-emission tomography (PET) was done which showed hypermetabolic neck lymph nodes, multiple thin-walled cystic lung lesions (compatible with lung metastases) and multiple lytic bone metastases. Hence, the diagnosis of metastatic angiosarcoma was established.

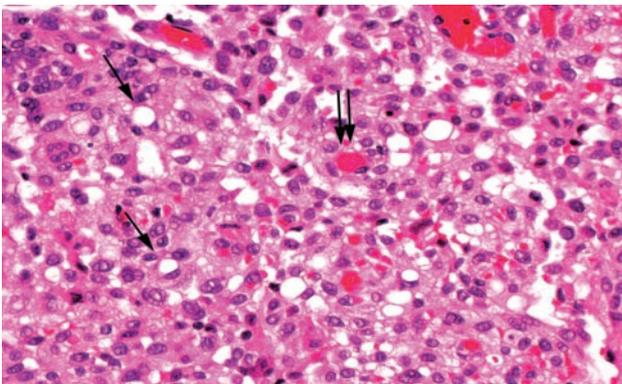
Our patient was referred to the oncologist and palliative radiotherapy to thoracic spine for pain control and impending cord compression was planned for her. Unfortunately, our patient's condition gradually deteriorated and finally succumbed five months after initial presentation.



**Figure 3.** (5x objective): Infiltrative irregular vascular channels throughout the dermis.



**Figure 4.** (20x objective): The vascular channels are lined by atypical endothelial cells with hyperchromatic, enlarged nuclei.



**Figure 5.** (40x objective): There are solid areas which are composed of epithelioid endothelial cells with cytoplasmic vacuoles (single arrow). Some vacuoles contain red blood cells (double arrow).

## Discussion

Angiosarcoma is a subtype of soft tissue sarcoma. It was first described by Caro & Stubenrauch in 1945. It is an aggressive malignant endothelial cell tumour of vascular or lymphatic origin with a poor prognosis. The most common presentation is a cutaneous form affecting head, neck or scalp in elderly white men.

Angiosarcoma can be classified as cutaneous angiosarcoma, lymphoedema-associated angiosarcoma (Stewart-Treves syndrome), radiation-induced angiosarcoma, primary breast angiosarcoma and soft tissue angiosarcoma. It constitutes 2% of soft tissue sarcomas and 5.4% of cutaneous soft tissue sarcomas.<sup>1</sup> It can develop at any age, more commonly in elderly over 70 years old. It commonly affects the head and neck regions (27.0%), followed by the breast (19.7%), extremities (15.3%), trunk (9.5%), liver (6.0%), heart (4.7%), bone (3.6%) and spleen (2.6%).<sup>1</sup>

Risk factors for developing angiosarcoma include radiation, chronic lymphoedema (Stewart-Treves syndrome), post-surgery or radiotherapy (e.g. post breast carcinoma therapy), exposure to exogenous toxins (e.g. vinyl chloride, thorium dioxide, arsenic, anabolic steroids, foreign bodies) and familial syndromes (e.g. neurofibromatosis type 1, mutation of *BRCA1* or *BRCA2* genes, Maffucci syndrome, Klippel-Trenaunay-Weber syndrome).<sup>1</sup>

Cutaneous form of angiosarcoma initially presented as a bruise or a raised purplish-red papule on the central face, forehead or scalp. Facial swelling and oedema may be present. Increasing tumour size, tissue infiltration, oedema, tumour fungation, ulceration, haemorrhage can all develop. In lymphoedema associated angiosarcoma (Stewart-Treves syndrome), firm coalescing violaceous nodules or indurated plaque on a background of non-pitting oedema is the usual presentation. More than 90% of cases arise after mastectomy and lymph node dissection. Inner aspect of the upper arm is the most common

site of involvement. The duration of lymphoedema prior to development of angiosarcoma varies from 4 to 27 years.<sup>2</sup> Post-irradiation angiosarcoma presents as infiltrative plaques or nodules in or near the radiation field. It usually follows radiation for gynaecologic malignancies or breast carcinoma. The lesions can occur 4 to 40 years after irradiation.<sup>3</sup> Angiosarcoma of soft tissue occurs in the extremities, retroperitoneum and abdominal wall. Thirty three per cent of patients have evidence of recent haemorrhage or coagulopathy, including anaemia, persistent haematoma, haemothorax, haemorrhagic ascites and gastrointestinal bleeding.<sup>3</sup> Angiosarcoma metastasises via the haematogenous route to lung, pleura, liver, bone or lymph nodes.

The histopathology of angiosarcoma depends on the areas of tumour differentiation.<sup>2</sup> In well differentiated areas, there is an anastomosing network of sinusoidal vessels lined by a single layer of endothelial cells of slight to moderate nuclear atypia. These vascular sinusoids split apart collagen bundles and groups of adipose cells. In less well differentiated areas, endothelial cells with more pronounced nuclear pleomorphism and mitotic activity pile up forming papillary projections. In poorly differentiated areas, the luminal formation is non-apparent. There is high mitotic activity mimicking high grade sarcoma or melanoma. Areas of haemorrhage or necrosis can occur. Endothelial markers (von Willebrand factor, CD34, CD31, *Ulex europaeus* agglutinin 1, vascular endothelial growth factor (VEGF)) are expressed in angiosarcoma.<sup>1</sup> The absence of S100, human melanoma black 45, and melanoma antigen help to distinguish it from melanoma. The identification of high concentration of the cytokine vascular endothelial growth factor A (VEGF-A) and three subtypes of VEGF receptors helps the development of vascular targeted therapies which will be discussed later.

Table 1 shows the TNM staging system for soft tissue sarcoma according to the International Union Against Cancer and American Joint

Committee on Cancer (UICC/AJCC) system. The overall 5 year survival of angiosarcoma is 35%<sup>1</sup> and the median survival of localised disease is 7 months.<sup>4</sup> The possible poor prognostic factors include tumours larger than 5 cm, high tumour grade, old age, metastatic disease at presentation, angiosarcoma of viscera (liver or heart), retroperitoneal disease and radiation induced disease, etc.<sup>1</sup> Diagnostic evaluations include skin biopsy, magnetic resonance imaging, computed tomography imaging and PET imaging. The value of sentinel lymph node biopsy is unknown.

For localised disease, radical surgery with complete resection is the first line treatment. However, margin involvement is common due to the invasive and multifocal nature of angiosarcoma. Wide excision margin is therefore recommended despite the fact that it is sometimes difficult to achieve because of diffuse tissue infiltration, tumour location (e.g. cardiac angiosarcoma), and relation of tumour to other structures (e.g. head and neck tumours). Due to high risk of local recurrence, large dose adjuvant radiotherapy (>50 Gy) is recommended.<sup>5</sup> There is no convincing evidence to support the use of

**Table 1.** TNM staging system for soft tissue sarcoma (including angiosarcoma). International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC) system

Tx	Primary tumour cannot be assessed
T0	No primary tumour found
T1	Tumour ≤5 cm diameter (T1a superficial; T1b deep)
T2	Tumour >5 cm diameter (T2a superficial; T2b deep)
Nx	Cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement
Mx	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

adjuvant or neoadjuvant chemotherapy in localised disease.

For metastatic diseases, cytotoxic chemotherapy (anthracyclines, ifosfamide, taxanes) is employed. However, its use is limited by the comorbidities in elderly patients and treatment related toxicity. The median progression free survival varies from 3.7 to 9.5 months.<sup>6-8</sup>

The use of anti-angiogenic molecules in treating angiosarcoma is studied in several phase 2 trials. Agents used include bevacizumab, a VEGF-A monoclonal antibody, and sorafenib, a tyrosine kinase inhibitor targeting VEGF receptors. The median progression free survival varies from 3.8 to 4.7 months and the median overall survival varies from 13.5 to 14.2 months.<sup>9,10</sup> Further studies are required to justify their efficacies in the treatment of angiosarcoma. Other potential treatment options reported include thalidomide, interferon- $\alpha$  and interleukin 2.

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