

Original Article

Cutaneous angiosarcoma: a case series in Hong Kong 皮膚血管肉瘤：香港的個案系列

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Background: Cutaneous angiosarcoma is a rare high grade malignant neoplasm in skin of endothelial differentiation. About 50% of cutaneous angiosarcoma affects head and neck region. **Objective:** To report a case series of primary cutaneous angiosarcoma in Hong Kong focusing in the clinical presentation and demographic features. **Materials and method:** Case records of patients from 2000 to 2009 with histopathological confirmation of the diagnosis of angiosarcoma were retrieved from the Social Hygiene Service clinics of the Department of Health of Hong Kong. **Results:** A total of 7 patients with primary cutaneous angiosarcoma were found. All patients were elderly with the age range from 72 to 91 years and a male predominance. Most patients could only be offered with palliative radiotherapy due to extensive disease upon presentation. The prognosis was generally poor. At the time of preparation of this manuscript, three patients has passed away and only one patient remains in remission. **Conclusion:** Cutaneous angiosarcoma is a high grade malignant neoplasm that mainly affected elderly men with poor prognosis. The tumor can mimic benign skin condition at the early stage and cause diagnostic delay. Clinicians should be alert of the diagnosis especially for suspicious lesions in the head and neck region in elderly patients so as to arrive at an early diagnosis.

背景：皮膚血管肉瘤是一種源自血管內皮分化的罕見高度惡性腫瘤，約五成的腫瘤發生在頭頸部位。**目的：**報告香港的原發性皮膚血管肉瘤一系列病例，並聚焦於臨床表現及人口學特徵的分析。**取材及方法：**檢索由二千年至二零零九年香港衛生署轄下社會衛生科的病歷檔案並抽取有組織病理學確診之皮膚血管肉瘤病患資料。**結果：**期間發現為數七人的原發性皮膚血管肉瘤病患，全為年長患者，年齡介乎七十二歲至九十一歲，並以男性居多。由於大多數患者求診時已屬廣佈期患情，故只能接受症狀緩解性的放射線治療。此病的預後一般都不容樂觀，在準備此原稿之

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時，已有三位病人離世，只得一名患者維持病愈狀況。**結論：**皮膚血管肉瘤是一種主要影響年老男士及預後欠佳的高度惡性腫瘤。由於早期病情可能會與良性皮膚狀況相類混淆，以致延醫誤診；故醫者應對此病保持警惕，尤其是年老患者的頭頸可疑患處，以求能作出早期診斷。

Keywords: Cutaneous angiosarcoma, elderly, head and neck

關鍵詞：皮膚血管肉瘤，年長患者，頭頸部位

Introduction

Angiosarcoma (AS) is a rare high grade malignant neoplasm of endothelial differentiation. It has a predilection for skin and superficial soft tissue although it can occur in various anatomic sites such as the heart, aorta, liver, bone and breast. Cutaneous angiosarcoma (CA) accounts for 60% of cases of angiosarcoma. These include primary CA and secondary CA caused by previous irradiation, chronic lymphoedema and pre-existing vascular malformation. About 50% of cutaneous angiosarcoma affect the head and neck region in elderly men, in particular the scalp area.¹ There is also a strong predilection for Caucasians. The clinical presentation varies greatly from early ecchymosis-like patch to advance tumourous nodules with ulceration and haemorrhage.

There is currently no local data or series available regarding the epidemiology of this tumor because of its rarity. This retrospective series serves to summarize the clinical features and diagnostic pitfalls encountered in this tumor so as to alert the clinicians for early detection of this high grade malignancy.

Materials and methods

The case records in Social Hygiene Service of the Department of Health of Hong Kong were reviewed and a total of seven patients with histopathological confirmation of primary cutaneous angiosarcoma were found between 2000 and 2009. They were seen in three clinics of the Social Hygiene Service, namely Yaumatei

Dermatological Clinic, Tuen Mun Social Hygiene Clinic and Yung Fung Shee Dermatological Clinic. After reviewing the case records, the demographic data, clinical features, management and outcome of patients were traced and recorded for presentation. Angiosarcoma arising from previous irradiated area, area with pre-existing vascular malformation or related to lymphoedematous extremity were excluded.

The case series

Demographic features

All patients were referred from primary care physicians for consultation. The demographic and clinical features of the patients were listed in Table 1. The age of patients ranged from 72 to 91 years upon presentation to our service. The mean age is 78.7 years and the median is 77 years. There were five male and two female patients with male to female ratio at 2.5:1. The patients had various medical diseases, the most common being hypertension, which was present in four out of seven patients.

Site of lesion and symptoms

The most common site of lesion was the head. Six patients (86%, patient 1,3,4,5,6,7) had lesions located in the scalp/forehead region. Patient 2 had multiple lesions over chest wall. None of the patients had previous irradiation or vascular abnormality in the area.

The mode of presentation was listed in Figure 1. The most common presentation was enlarging nodule(s), which was present in six patients (86%). Five patients (71%) had multiple nodular lesions

Table 1. Demographic, clinical and outcome features of patients

Patient: age (years)	Gender	Comorbidities	Lesion location & type	Diameter	Date lesions noted	Date of referral	Clinical impression	Date of confirmed diagnosis	Management	Outcome
Patient 1 83 years	Male	DM	Forehead Multiple nodules with discharge	Largest 4 cm	Jan 2002	Nov 2002	Carbuncle	Jan 2003	RT	Head, neck and lung metastases Died May 2005
Patient 2 72 years	Male	AF, HBsAg +	Chest Multiple nodules	Not recorded	Oct 2004	Dec 2004	Lymphoma	Dec 2004	Refer to surgery and oncology	Unknown
Patient 3 74 years	Female	HT	Scalp Multiple nodules with ulcer	Largest 2.5 cm	Sep 2005	May 2006	Angiosarcoma	May 2006	WLE	Lung metastases Died Oct 2006
Patient 4 73 years	Male	HT	Scalp 2 nodules with erosion	0.5 cm & 1 cm	Nov 2005	Jun 2006	Angiosarcoma	Jun 2006	WLE+RT	Remission
Patient 5 77 years	Female	AF, DM, HT, proteinuria	Scalp Single nodule with erosion	0.5 cm	Apr 2006	Nov 2006	Pyogenic granuloma	Nov 2007	RT	Multifocal scalp and face disease
Patient 6 91 years	Male	HT	Scalp Multiple nodules with ulcer	5 cm	Oct 2008	Jan 2009	Angiosarcoma	Jan 2009	RT	Extensive head and neck disease Died May 2009
Patient 7 81 years	Male	Nil	Forehead Single plaque with ulceration	2.5 cm	Apr 2009	Aug 2009	Angiosarcoma	Sep 2009	Refer to surgery	Unknown

AF: atrial fibrillation; HT: hypertension; DM: diabetes mellitus; HBsAg+: Hepatitis B carrier; RT: radiotherapy; WLE: wide local excision

upon presentation to our service, patient 5 had a single nodule in right temporal scalp area on first presentation and patient 7 presented with a single ulcerative plaque at left forehead. Another common symptom noted in the medical record was bleeding from the lesion. It occurred in six patients (86%, patient 2,3,4,5,6,7). Patient 1 presented with purulent discharge from the mass. Other symptoms include itch (patient 3,4,6) and pain (patient 1,2).

Time of presentation and diagnosis

The time lapse between lesions noticed by patient and referral to our service ranged from two months to ten months. The diagnosis of AS was confirmed within a short period of time (patient 2,3,4,6,7 was diagnosed within one month and patient 1 was diagnosed within 2 months) after referred to our service with the exception of patient 5.

Patient 5 was initially referred to our service for a single nodule with occasional bleeding in right temporal scalp area for seven months (Figure 2). The clinical impression was pyogenic granuloma and a shave biopsy was performed. The initial histopathology reported "anuevrysmal dermatofibroma". The biopsy wound was healed eventually and the patient was discharged. Patient 5 was subsequently referred to us eight months later with a recurrence of erosive lesion in right forehead area (Figure 3). Incisional skin biopsy performed and revealed poorly differentiated

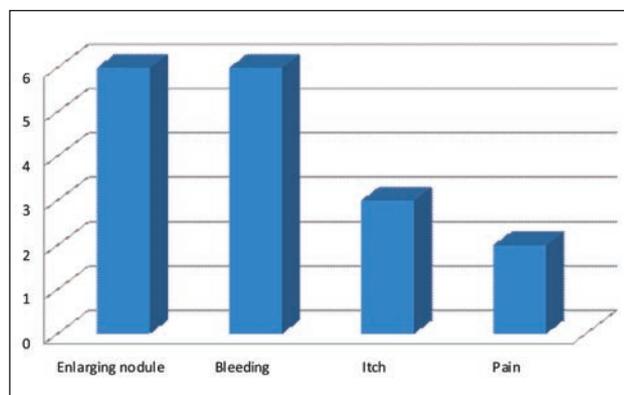


Figure 1. Symptoms of patients upon presentation.

angiosarcoma. She was also found to have multifocal lesions in scalp and face which were not amendable to surgery. In view of the old age and comorbidities, she was offered palliative radiotherapy.



Figure 2. Pyogenic granuloma-like nodule in right temporal scalp of patient 5 upon initial presentation.



Figure 3. Ulcerative nodule with surrounding erythematous to violaceous patch in right temporal scalp of patient 5 in subsequent presentation.

Initial clinical diagnosis

The initial clinical diagnosis was malignant neoplasm in five patients (71%), in which angiosarcoma was suspected in four patients and lymphoma in one patient. Patient 1 had the initial diagnosis of carbuncle and patient 5 had the initial diagnosis of pyogenic granuloma. Patient 3 was initially seen by private practitioner with the diagnosis of scalp seborrheic keratosis. The lesion was biopsied and the histology failed to reveal the true nature of the lesion. When she was seen by our clinic, multiple darkish ulcerative nodules were present over the scalp and angiosarcoma was suspected (Figure 4). Urgent skin biopsy was performed and confirmed the diagnosis of CA. Patient 6 presented with typical advanced disease over bilateral parietal scalp with multiple local metastases (Figure 5).

Histopathology

The histopathology in all the diagnostic biopsies revealed similar pattern. The tumor cells exhibited infiltrative dissecting growth in the dermis and subcutis. They formed abnormal and irregular vascular channels. There was prominent intralesional haemorrhage. The tumor cells were mainly of oval to spindle shape with pleomorphic nuclei and prominent mitotic figures. Immunohistochemical stain revealed CD31 positivity in patient 1,3,4,7 and CD34 positivity

in patient 2,4,5,6, confirming their endothelial nature.

The histopathology of the biopsy specimen of patient 5 worth further discussion. In the first biopsy of the nodular pyogenic granuloma-like lesion, the low power view showed a nodular lesion with whorls of spindle cells with dissecting vascular channels in the periphery (Figure 6). High power view showed intersecting fascicles mimicking Kaposi sarcoma (Figure 7). There was only mild cytological atypia (Figure 8). In the second biopsy, the low power view showed tumor diffusely



Figure 5. Advanced disease in patient 6 with multiple darkish ulcerative nodules and active haemorrhage was noted.



Figure 4. Multiple darkish ulcerative nodules in left parietal scalp of patient 3.

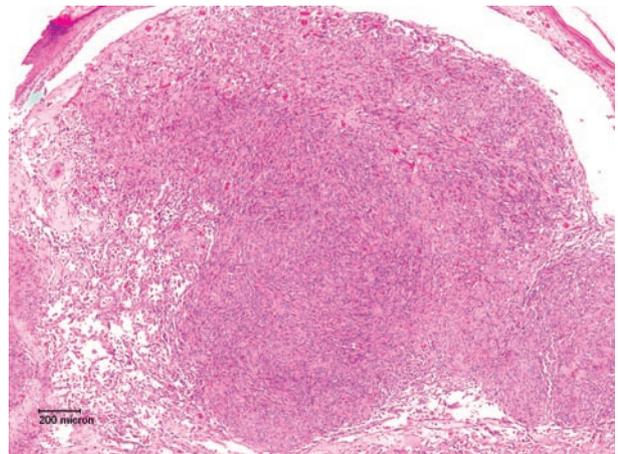


Figure 6. 1st biopsy of patient 5, low power view: nodular lesion with whorls of spindle cells, note the dissecting vascular channels in the periphery. (H&E)

infiltrating the dermis with dissecting vascular channels in the deep portion of the specimen (Figure 9). The high power view showed the dissecting channels lined by pleomorphic tumor cells typical of angiosarcoma (Figure 10). Review of the initial biopsy in patient 5 showed lobular proliferation of spindle cells with slit like vascular spaces showing superficial resemblance to pyogenic granuloma. In retrospect, complex anastomosing vascular channels were found in the periphery of these lobules raising suspicion for a malignant vascular tumor.

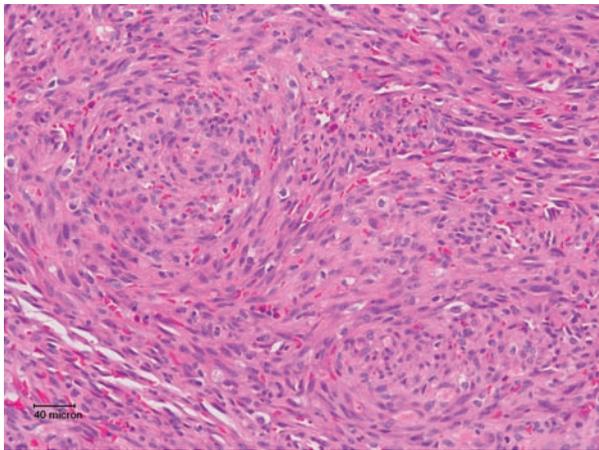


Figure 7. 1st biopsy of patient 5, high power view: note the intersecting fascicles mimicking Kaposi sarcoma. (H&E)

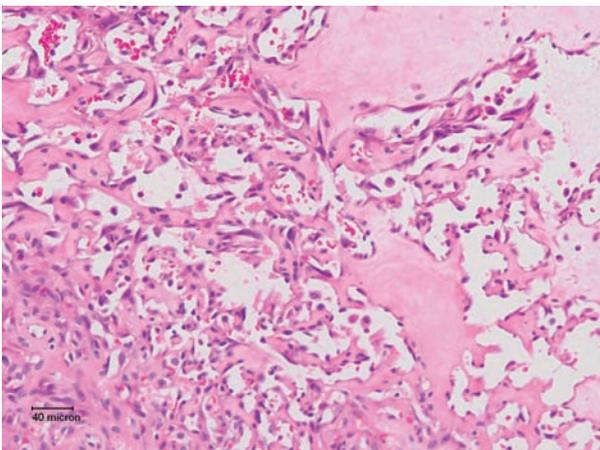


Figure 8. 1st biopsy of patient 5, high power view: the dissecting vascular channels with mild cytological atypia. (H&E)

Management

Three patients (patient 1,5,6; 43%) had extensive disease over the head and face area on presentation and were inoperable. They were offered palliative radiotherapy. Two patients (patient 3,4; 29%) were offered wide local excision of the tumors and patient 4 also received post-op adjuvant radiotherapy. Patient 2 and 7 defaulted follow-up and the management and outcome were unknown. Chemotherapy was not offered to patients in

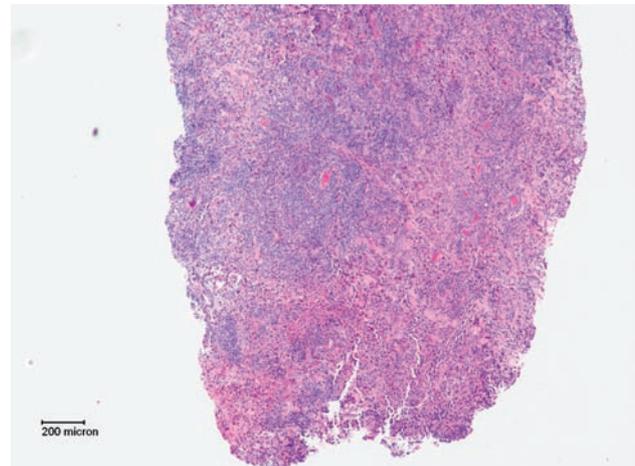


Figure 9. 2nd biopsy of patient 5, low power view: the cellular tumor diffusely infiltrating the dermis. There is dissecting channels in the deep portion of the specimen. (H&E)

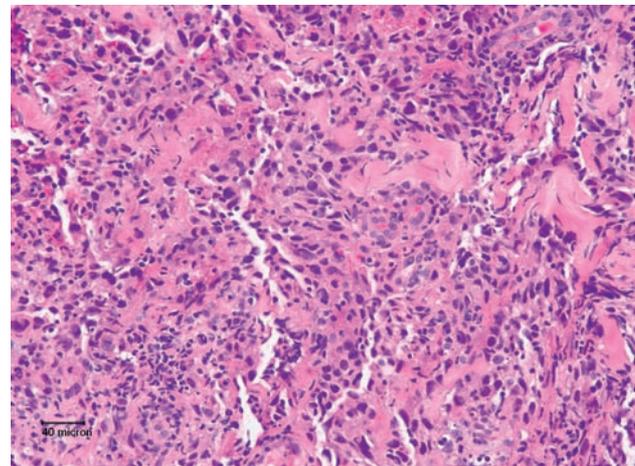


Figure 10. 2nd biopsy of patient 5, high power view: dissecting vascular channels lined by pleomorphic tumor cells typical of angiosarcoma.

this series due to advanced disease and age of patients, comorbidities, patient reluctance and doubtful survival benefit.

Outcome

Three mortalities were noted in the series. Patient 1 had multiple local metastases upon presentation and lung metastases afterwards. He was offered palliative radiotherapy and he passed away two years and four months after confirmation of the diagnosis. Patient 3 had wide local excision done but she suffered from lung metastases with persistent pleural effusion. She passed away five months after the diagnosis. Patient 6 passed away four months after the diagnosis, he had extensive disease upon presentation and palliative radiotherapy was offered.

Patient 5 suffered from multifocal disease in head and face and palliative radiotherapy was offered. Patient 4 is currently in remission after surgery and adjuvant radiotherapy given since 2006.

Discussion

Cutaneous angiosarcoma (CA) was first reported in detail by Caro and Stubenrauch in 1945.² In 1948, Stewart and Treves described the association between angiosarcoma and post-mastectomy lymphoedema, thereafter the Stewart-Treves syndrome was named.³ Later in 1964, Jones characterized CA that primarily affected the scalp and face of elderly male.⁴ CA is rare and accounts for less than 1% of all sarcomas. It is classified into primary form and secondary form, the primary form being more common. Apart from the well-recognized association of secondary CA with chronic lymphoedema, post-irradiation and pre-existing vascular malformation, no definite predisposing factors could be identified for the primary CA. The common presentation in the head and neck region raised the suspicion of excessive ultraviolet exposure as risk factor but is inconclusive as some investigators pointed out that in people with

excessive ultraviolet exposure CA is still a very rare malignancy.

All our patients were over 70 years of age and the male to female ratio was 2.5:1. This series reconfirmed others experience that CA is a malignancy of elderly with male predominance.^{1,5-8} However age and gender were not shown to be a prognostic indicator in other series.^{1,5}

The anatomic location of tumor in this series was mainly in the scalp region, in six out of seven patients (86%). This result was also concordant with other series.^{1,5} It was shown in other studies that anatomic location did not affect the survival.

The most common presentation in this series was enlarging violaceous to darkish nodule, mostly multifocal. This was reported by other studies as well.^{1,9,10} The lesions were present for only a few months (range 2-10 months) before consultation and some of them evolved quite quickly to become multiple nodules. Bleeding from the lesions was also another common complaint, which was noted in six patients (86%). This indicates the vascularity of the tumor and the reason why it mimics a pyogenic granuloma both clinically and histologically. This can cause diagnostic difficulty and delay the biopsy for confirmation as happened in patient 5. Secondary infection of the tumor can also mask the diagnosis clinically and caused delay in a confirmatory biopsy which was the case in patient 1.

According to our records, in 4 out of the 7 patients the diagnosis of CA was already on the top of the earliest list of differential diagnosis. Patient 2 gave the impression of malignant lymphoma which also prompted the clinician for urgent biopsy and action. Patient 1 gave the initial impression of carbuncle which was treated with incision and drainage and course of antibiotics. However the lesions fail to response to treatment and increase in size and number. A skin biopsy was then arranged and confirmed the diagnosis. The

clinical presentation and course of disease in patient 5 had been discussed in the previous section.

The histopathological features of typical prominent lesion of CA along with positive immunohistochemical stain of CD31 or CD34 creates little problem in diagnosis. It is the early lesion that forms the diagnostic pitfall sometimes even with the help of immunohistochemical staining. A high index of suspicion by clinician and pathologist was essential.

The outcome of CA was generally reported to be poor with a five year survival rate of 10-35%.^{1,10} Our series agrees with this observation and three out of seven patients has passed away at the time of preparation of this manuscript. Patient 1 and patient 6, who accounted for two of the mortalities, was at more advanced age of 83 years and 91 years respectively, older than the mean age of 78.7 years in the series. Patient 3 died of extensive lung metastasis with persistent haemorrhagic pleural effusion.

In the literature review, demographic factors and anatomic location were not shown to be of prognostic significance.^{1,11,12} The diameter of tumor greater than 5 cm at time of presentation, presence of positive surgical margin predicts poor prognosis. This was reflected by the course of disease in patient 6, who passed away four months after diagnosis, in which the largest tumor size was 5 cm in diameter. Patient 1 and 3 who reported death, also had larger tumor size of 4 cm and 2.5 cm in diameter respectively (the diameter of tumor upon presentation was listed in Table 1). Metastasis, tumor recurrence and depth of invasion was also found to be significant predictors of poor outcome in the literature.¹ This was also reflected in patient 1, 3 and 6 in which lung and extensive local metastases were documented. The surgical margin, tumor recurrence and depth of invasion were not recorded in the case records.

The treatment modality was mainly surgery and radiotherapy in our series. Four patients (57%) were offered radiotherapy, in which three were considered palliative. Two of the patients died after palliative radiotherapy (patient 1 and 6). Patient 5 still survived at the present moment without significant morbidity, over two years after confirmed diagnosis. Patient 4 was offered adjuvant radiotherapy after wide local excision, he was considered in remission and disease free up to the present moment, three and a half years after confirmed diagnosis. Patient 2 and 7 were lost to follow-up after referral to surgery and oncology department.

Other treatment modality include chemotherapy with various agents such as doxorubicin,¹ cyclophosphamide,¹ methotrexate,¹ vincristine,¹ paclitaxel^{1,10,13} and interferon-alfa¹⁴ had been reported in different series with variable success. Large controlled study is not available due to the rarity of the tumor.

Although surgical treatment remains the first option for CA, to achieve a negative surgical margin is often very difficult. Wide local excision of clinically evident tumor in patients and follow by wide field irradiation might be the recommended treatment if condition allows.^{6,7,9} This was the management employed in patient 4 which resulted in remission. For those where surgical treatment cannot be offered, radiotherapy alone can offer some disease control. Treatment of metastatic disease is mainly palliative as all patients will eventually died of the disease.¹

Conclusion

Primary cutaneous angiosarcoma is a rare high grade malignant neoplasm with guarded prognosis. The affected individuals locally have the characteristics of old age and male predominance. The commonest affected anatomic region was the scalp and enlarging nodules with

haemorrhage were the commonest presentations. Most patients presented with advanced disease and the treatment modality was limited. CA can mimic other benign cutaneous pathologies and the diagnosis can only be reached with histopathology. Delay in diagnosis is not uncommon in early stage of disease. The optimal management strategy currently recommended for cure is wide local excision followed by wide field irradiation.^{6,7,9} Palliative irradiation offered for advanced disease showed reasonable disease control in individual patient. Chemotherapy is useful in individual patient but larger studies are required to determine the significance.

In conclusion, primary cutaneous angiosarcoma, especially in its early stage, is a disease that requires high index of suspicion by the clinicians and pathologists in order to arrive at an early diagnosis.

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