

## CASE REPORT

## Mammary Angiosarcoma in an Adolescent : A Case Report

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### ABSTRAK

Angiosarkoma payudara adalah tumor malignan yang jarang dijumpai dan sangat agresif yang berpunca dari salur darah. Ia terbahagi kepada 2 jenis; angiosarkoma primer yang terbentuk dengan sendirinya dan angiosarkoma sekunder yang terhasil akibat komplikasi selepas radioterapi atau limfedema kronik. Kami membentangkan kes seorang gadis yang berumur 19 tahun, telah hadir dengan ketulan yang besar di payudara kanannya untuk tempoh 9 bulan. Biopsi teras ketulan itu dilaporkan sebagai angiosarkoma. Dia tidak mempunyai sebarang penyakit di bahagian payudara sebelum ini. Dia telah menjalani mastektomi kanan, diikuti dengan radioterapi adjuvan. Dia telah dikesan mengalami tumor itu yang telah merebak ke kulit kepala dan tengkoraknya 5 bulan selepas pembedahan dan dia sedang menjalani kemoterapi paliatif. Tidak terdapat garis panduan antarabangsa yang jelas berkaitan rawatan angiosarkoma payudara disebabkan penyakit ini jarang dijumpai. Rawatan utama adalah pembedahan, di mana mastektomi adalah disyorkan. Radioterapi dan kemoterapi kadangkala diberikan dalam usaha untuk mengelak atau merawat penyakit yang berulang atau yang telah merebak.

Katakunci: Angiosarkoma payudara; mastektomi; merebak ke tengkorak; remaja

### ABSTRACT

Mammary angiosarcoma is an extremely rare and highly aggressive malignant tumour of vascular origin. It can be divided into 2 types; primary angiosarcoma which develops de-novo and secondary angiosarcoma which occurs as a

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complication of post-radiotherapy or chronic lymphoedema. We present a case of a 19-year-old adolescent with a large right breast mass for the duration of 9 months. The core biopsy was reported as an angiosarcoma. She did not have any previous breast pathology. She underwent a right mastectomy, followed by adjuvant radiotherapy. She developed scalp and skull metastases 5 months post-surgery and was currently undergoing palliative chemotherapy. There is a lack of international consensus on the management of mammary angiosarcoma due to its rarity. The main modality of management is surgery, preferably mastectomy. Radiotherapy and chemotherapy are sometimes given in an attempt to prevent or treat local recurrence and metastasis.

Keywords: Adolescent; mammary angiosarcoma; mastectomy; skull metastases

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## INTRODUCTION

Mammary angiosarcoma is an extremely uncommon, highly aggressive tumour of vascular origin, with the incidence of 1% of breast tumours and 8% of breast sarcomas. It is divided into 2 types, primary and secondary angiosarcoma. Primary angiosarcoma develops de-novo, while secondary angiosarcoma develops as a sequelae of regional radiotherapy in the management of breast carcinoma, and as a complication of chronic lymphoedema, known as Stewart Treves Syndrome. Both types have malignant behaviour and poor prognosis (Abbad et al. 2017; Kunkiel et al. 2018; Mouhoub et al. 2019; Nascimento et al. 2008; Rosen et al. 1988; Tato-Varela et al. 2016). Primary angiosarcoma occurs sporadically in women aged 30 to 50 years, but more commonly during the third or fourth decade of life (Cao et al. 2012; Dashevsky et al. 2013; Raju et al. 2014). Based on our literature review, we believe our patient is one

of the youngest with this malignancy. We present a case of mammary angiosarcoma in an adolescent female.

## CASE REPORT

A 19-year-old Malay nullipara presented with a large right breast mass for the past 9 months. Two years later, her 55-year-old mother was diagnosed with a breast carcinoma. The patient was referred from a private centre, where a core biopsy had been performed and was reported as an angiosarcoma. A staging PET-CT scan was done and showed no distant metastasis. On examination, there was a large mass occupying the entire right breast, measuring 15 cm x 10 cm, with no skin changes or nipple retraction (Figure 1). She and her family members were counselled and agreed for her to undergo a right mastectomy. Intra-operatively, the mastectomy had been performed right down to the pectoralis muscle with no gross tumour infiltration into the muscle. The estimated intra-operative



FIGURE 1: Preoperative photo of the patient with the right breast mass

blood loss was 500 ml. The patient's haemoglobin however, dropped from the pre-operative level of 11 g/dL to 7.7 g/dL post-operatively. She required transfusion of 2 units of packed cells, and her haemoglobin increased to 8.1 g/dL. She was discharged home with a surgical drain in situ on the 3<sup>rd</sup> post-operative day. This was because she still had 60-80 ml blood drained daily but the volume was expected to decrease. On review in clinic 4 days later, her drain chart showed that

the daily volume of blood loss had remained the same and the dressing was soaked in blood. She complained of lethargy and dizziness and her haemoglobin level was 7.8 g/dL. She was readmitted and underwent wound exploration, to look for the source of bleeding. Intra-operatively, a small spurting arteriole was found which was ligated. She was transfused 1 pint packed cells intra-operatively and haemoglobin increased to 8.5 g/dL. Her symptoms resolved.

The cut section of the mastectomy specimen from its deep surface, showed a large irregular unencapsulated mass at the retro-areolar area, measuring 13.5 cm x 12.0 cm x 7.5 cm.

Her total operative blood loss was hidden; due to these massive blood vessels in the tumour. The tumour had reddish to brownish vascular cut surfaces with areas of necrosis (Figures 2). The microscopic examination (Figures 3) revealed areas of atypical anastomosing vessels, with a mixture of endothelial tufting and solid spindle cell components, corresponding to a poorly differentiated angiosarcoma

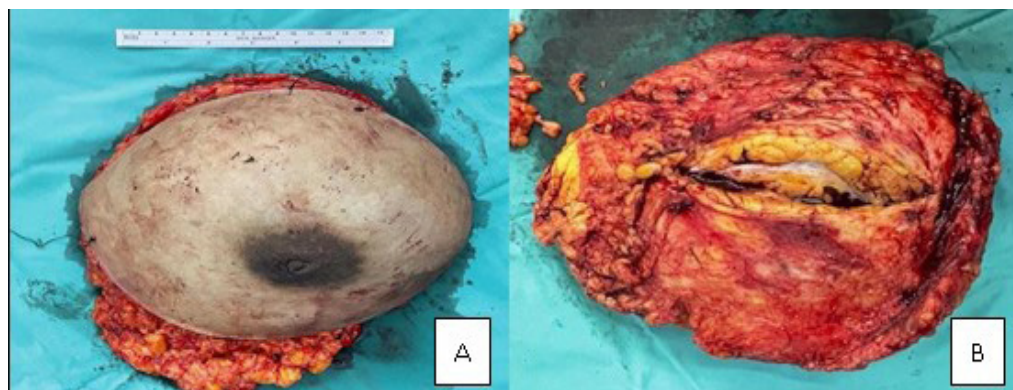


FIGURE 2: (A) Right mastectomy with tumour 13.5 x 12 x 7.5 cm (anterior view); (B) Tumour bivalved showed many dilated blood vessels and pockets of blood within (posterior or deep surface).

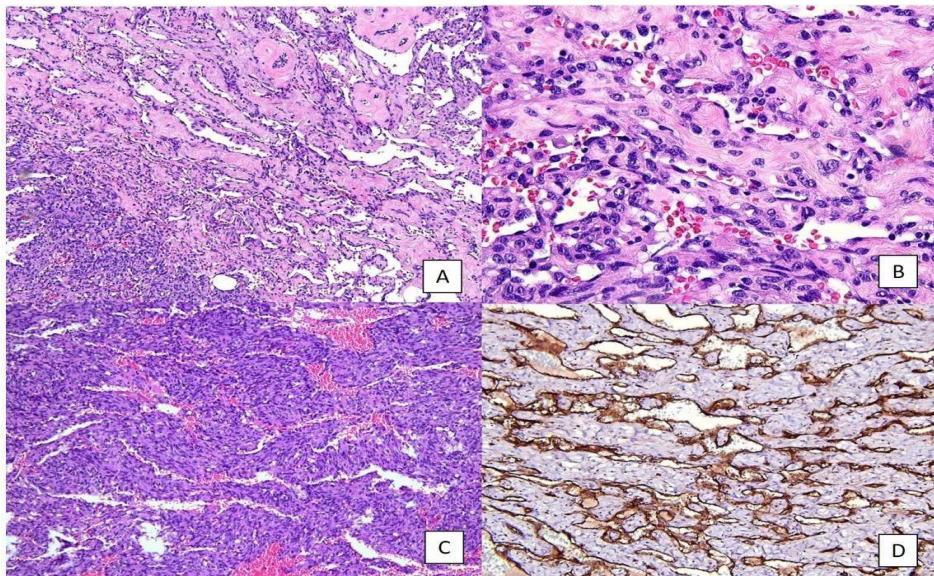


FIGURE 3: Histological slides of the right breast. (A) The tumour was composed of well-formed, small to medium-sized anastomosing vessels with dilated, compressed or angulated lumens, 100x; (B) The vessels were lined by flattened to plump neoplastic endothelial cells with minimal atypia, exhibiting vesicular to hyperchromatic nuclei, occasional conspicuous nucleoli and ample cytoplasm, 400x; (C) High grade solid component,100x; (D) The neoplastic cells were positive for CD31

(Grade 3). Areas of haemorrhage, necrosis and thrombosis were observed too. The neoplastic cells were immunohistochemically positive for CD31. There was no concurrent ductal carcinoma-in-situ or invasive carcinoma. The resection margins were clear of malignancy; with the closest, the deep margin, measuring 4 mm. At the breast multidisciplinary

team discussion, the decision was for her to undergo right chest wall adjuvant radiotherapy consisting of 50 Grays in 25 Fractions, to minimise local recurrence. There was no evidence of contralateral malignancy in the breast magnetic resonance imaging (MRI).

Five months post surgery and 3 months post chest wall radiotherapy, she presented with two scalp nodules

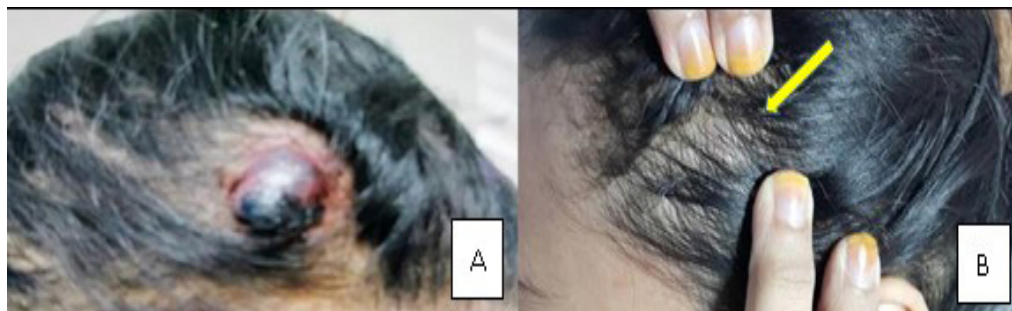


FIGURE 4: Scalp lesions at bilateral frontal regions; (A) Right frontal; (B) Left frontal (arrowed)

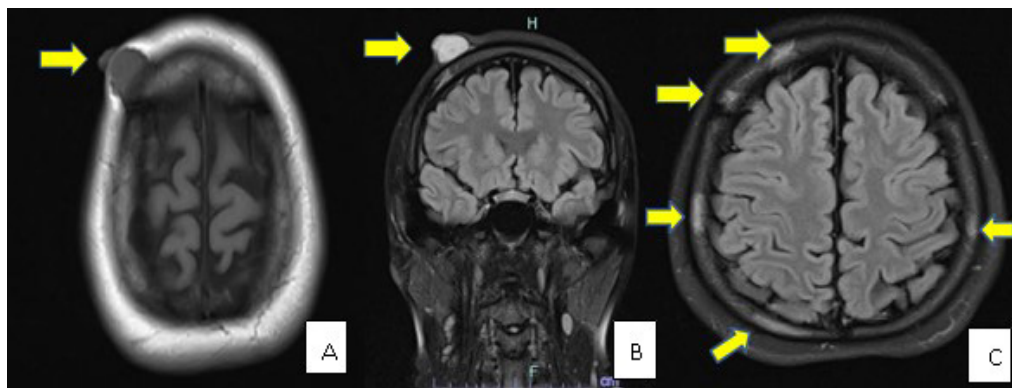


FIGURE 5: MRI brain showed multiple bone lesions in the skull vault at bilateral frontal, bilateral parietal and right occipital bones; (A) Right frontal cutaneous lesion with underlying bone involvement; (B) Right frontoparietal with no intracranial extension; (C) Right frontal, right frontoparietal, bilateral parietal and right occipital lesions

(Figures 4). On initial inspection, the provisional diagnosis made was infected sebaceous cysts and excision was discussed. However, as the larger one bled on contact, this increased clinical suspicion. A contrasted MRI brain was done which showed multiple bone lesions at the skull vault; at the right frontal, right frontoparietal, bilateral parietal and right occipital regions with no intracranial extension. (Figures 5). The right frontal cutaneous lesion which extended into the underlying bone, had a serpiginous flow void signal around it in keeping with vessels and heterogenous blooming artefact within it, suggestive of haemosiderin deposits. She underwent a whole-body PET-CT scan which showed two hypermetabolic subcutaneous scalp lesions concurring with the clinical findings. After a multidisciplinary discussion involving the breast surgeons, neurosurgeons and oncologists, it was decided for her to undergo 6 cycles of Paclitaxel.

## DISCUSSION

Mammary angiosarcoma was first described by Borrmann in 1907. It is classified into 2 types, primary and secondary angiosarcoma. Primary angiosarcoma arises de-novo, comprising 20% of all angiosarcoma. It occurs more commonly in women with age ranging from 30 to 50 years (youngest reported case was at 14 years old), arising within the breast parenchyma with infrequent skin invasion. Secondary angiosarcoma, which is the more common type, occurs in older women with a mean age of 65 years (Philip et al. 2018; Tato-Varela et al. 2016). It develops commonly as a consequence of post-operative radiotherapy for breast carcinoma and/or in a limb with chronic lymphoedema (Philip et al. 2018; Rosen et al. 1988). We believe that this was the second youngest reported case of primary mammary angiosarcoma.

The exact aetiology of mammary

angiosarcoma is unknown. Primary angiosarcoma occurs more commonly in younger women, usually sporadically, and 6-12% of them present during pregnancy or shortly after delivery, suggesting a hormonal effect. However, the immunoreactivity to oestrogen receptor is uncommon, the hormonal dependency is still undetermined. On the contrary, patients with secondary angiosarcoma usually have a history of previous radiation. The latency period post-radiotherapy is 5 to 10 years. It is postulated that radiation less than 50Gy contribute to secondary angiosarcoma, due to DNA damage and genomic instability, which usually involve the edge of the radiation fields. Radiation of at least 50Gy causes apoptosis (Ghareeb et al. 2016; Philip et al. 2018; Tato-Varela et al. 2016).

Those with sarcomas, such as osteosarcoma and leiomyosarcoma may be associated with heritable cancer predisposition syndromes such as Li Fraumeni Syndrome (gene TP53) and Hereditary leiomyomatosis and renal cell cancer syndrome (FH gene). However, those with mammary sarcoma and angiosarcoma have not been identified to belong to any particular syndrome of familial disease (Farid & Ngeow 2016).

The clinical presentation of those with mammary angiosarcoma is usually fullness of the breast, of insidious onset, or less commonly as a rapidly growing painless breast mass. If the mass is large and superficial, the skin of the breast may show a purplish-blue discolouration. Patients may present with manifestations of

consumptive coagulopathy, which is known as Kasabach-Merritt Syndrome (Philip et al. 2018; Rosen et al. 1988). This occurs due to bleeding into a rapidly growing angiosarcoma, resulting in a widespread activation of coagulation pathway. Simultaneous activation of systemic fibrin formation causes an increased generation of thrombi, along with an impaired anticoagulation mechanism and an impaired clearance of fibrin, resulting in thrombotic occlusion of small and medium sized vessels. Tumour cells express procoagulant factors and fibrinolytic inhibitors, causing a hypofibrinolytic state. These contribute to the development of disseminated intravascular coagulopathy (Alexandrova et al. 2014; Philip et al. 2018).

There are no pathognomonic features of angiosarcoma on mammogram and ultrasound. Ultrasound findings may show a heterogenous mass, which is similar to features seen in inflammation or infection, and may show signs of hypervascularity on colour Doppler (Philip et al. 2018). On mammogram, it may show an ill-defined mass without calcification, associated with overlying skin thickening. MRI is the main choice of radiological investigation for evaluation of the regional extent of the tumour and vascular nature of the lesion. Features of hyperintensity on T2 images may be displayed and there may be a rapid intense phase followed by washout. PET-CT scan is useful for staging (Bhosale et al. 2013; Mouhoub et al. 2019; Philip et al. 2018; Tato-Varela et al. 2016; Wu et al. 2019).

Preoperative diagnosis can be done by fine-needle aspiration cytology (FNAC) or core biopsy. However, the false negative rate is 37%. Excessive bleeding following biopsy may occur due to the highly vascular tumour (Abbad et al. 2017; Mouhoub et al. 2019). The Rosen 3-tier system classifies primary breast angiosarcoma into 3 grades; Grade I (low grade) demonstrates inter-anastomosing vascular channels through breast lobules and surrounding ducts, lined by hyperchromatic endothelial cells and exhibits minimal endothelial tufts. Grade II (intermediate grade) exhibits papillary formation with mitosis with or without solid or spindle cell foci, while Grade III (high grade) demonstrates prominent endothelial tufting, papillary formation, solid and spindle cell foci with numerous mitosis and blood lakes (Ghareeb et al. 2016; Mouhoub et al. 2019). Immunohistochemical stains for endothelial markers include CD31, CD34 and Factor VIII (von Willebrand factor). CD31 is the most sensitive and specific marker for angiogenic proliferation (Abbad et al. 2017; Mouhoub et al. 2019). Other differential diagnoses are benign haemangioma, malignant phyllodes, metaplastic carcinoma, fibrosarcoma and liposarcoma (Iacoponi et al. 2016; Mouhoub et al. 2019).

To date, there are only limited studies available, posing obstacles in developing the therapeutic recommendation for mammary angiosarcoma. The gold standard of management is surgery, mainly mastectomy. Breast conserving surgery is possible for those with small

tumours. Lymph node involvement is rare, about 0-5%, therefore, routine axillary dissection is not recommended (Iacoponi et al. 2016; Liberman et al. 1992; Mouhoub et al. 2019; Philip et al. 2018; Tato-Varela et al. 2016).

Mammary angiosarcoma has a high rate (30%) of local recurrence and metastasis. Metastasis occurs primarily by the haematogenous route to lungs, bones, liver, skin and contralateral breast. Pulmonary metastasis is most common. Adjuvant chemotherapy is recommended; consisting of anthracycline-based regime with ifosfamide or taxane-based chemotherapy. Gemcitabine may be given in metastatic disease as marginal efficacy has been demonstrated (Hirata et al. 2011; Penel et al. 2008, Pervaiz et al. 2008; Sher et al. 2007). Adjuvant radiotherapy improves local regional control but not consistently shows to improve survival (Pandey et al. 2015, Rosen et al. 1988). Tyrosine kinase inhibitor such as Imatinib may be used but is still largely experimental (Kunkiel et al. 2018; Mouhoub et al. 2019; Philip et al. 2018).

The prognosis depends on the tumour size, grade and status of the resection margin. Adverse prognostic indicators include tumour size more than 5 cm, high histologic grade, high mitotic rate and presence of necrosis (Iacoponi et al. 2016; Mouhoub et al. 2019; Philip et al. 2018). The 5 year survival rate for primary angiosarcoma is 40-55% and for secondary angiosarcoma is 43-88%. The 5 year disease-free rate in high grade tumours is 15%, intermediate grade is 70% and low grade is 78% (Cao et al. 2012;

Dashevsky et al. 2013; Ghareeb et al. 2016).

## CONCLUSION

We present a rare case of mammary angiosarcoma in an adolescent with rapid skull and cutaneous metastases. Angiosarcoma is diagnosed by triple assessment, but definitive diagnosis is based on the histopathology result. The main modality of management is a mastectomy. Extensive bleeding may occur due to its high vascular nature. Blood transfusion is often required, especially in large lesions. As it has high metastatic rate and local recurrence rate, adjuvant chemotherapy and radiotherapy should be given. She will need to be followed up 3-6 monthly. However, her prognosis is poor, considering her skull and cutaneous metastases are progressing despite the chemotherapy.

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