Section: Pathology

A case of cutaneous angiomyolipoma with review of the literature
M Ram¹, T Rodrigo¹, M Petkar¹

1. Department of Histopathology, Broomfield Hospital, Court Road, Broomfield, Chelmsford, Essex, UK.

Corresponding author:
Dr. Manisha Ram, MBBS, DNB (Pathology), FRCPath

Emails

M Ram: manisharam@nhs.net
M Petkar: mahir.petkar@meht.nhs.uk
T Rodrigo: thushara.rodrigo@meht.nhs.uk
Abstract

Angiomyolipomas (AML) are rare benign mesenchymal tumours. They are composed of an admixture of blood vessels, smooth muscle and adipose tissue and are often seen in the setting of tuberous sclerosis. Although typically presenting in the kidney, features considered diagnostic of AML can occur in extra-renal sites and therefore, this diagnosis cannot be excluded on the basis of site alone. Cutaneous AML has been rarely described in literature. The Cutaneous AML differs from renal AML in terms of circumscription, absence of epithelioid cells, male predominance and lack of association with tuberous sclerosis. The unique features of this lesion distinguish it from other lesions such as angiomyoma, angiolipoma, myolipoma, haemangioma and other mixed mesenchymal tumours.

We describe a case of AML presenting on the lip of an 85 year old male. To the best of our knowledge, this is the 22nd case of cutaneous AML reported in the English literature. As with all previously described cases, our patient did not present with the stigmata of tuberous sclerosis. AML should be considered within the differential for subcutaneous nodules and work-up for tuberous sclerosis should not be pursued when presenting in the skin.

Introduction

AMLs are benign tumours of either hamartomatous or mesenchymal origin, typically occurring within the kidney. They are composed of various amounts of fat, smooth muscle and blood vessels, affecting the kidney as a solitary or multicentric mass. Extrarenal AMLs are extremely rare and have been reported in the liver, nasal cavity, oral cavity, heart, colon, lung, spleen, lymph node, spermatic cord, penis, vagina, uterus, fallopian tube, abdominal wall, retroperitoneum, mediastinum, epidurally in the spine, subgalea aponeurotica and skin. Histologically, AML is a circumscribed nodule consisting of the classic triad: irregularly arranged sheets and interlacing fascicles of smooth muscle bundles, convoluted thick walled blood vessels and mature adipose tissue. Despite the histological similarity observed in renal and extrarenal AMLs, they differ in several ways from each other. Cutaneous AMLs are exceedingly rare and are often confused with angiolipomas and angioleiomyomas clinically. A third of renal AMLs are associated with tuberous sclerosis, but cutaneous AMLs are known to have no such association till date.

Report of case

Clinical findings

The patient was an 85 year old male with a past medical history of hypertension and gastric ulcer, for which he was on medication. He presented to the plastic surgery clinic with a non-painful, solitary nodule on the upper lip which had been present for many years, with recent increase in size. There was a history of bleeding upon getting caught while shaving. On physical examination, there was a dome shaped, rubbery, movable, non-tender, compressible partially cystic nodule with a bluish tinge. It had several obvious blood vessels traversing it which may have been responsible for the bleeding. There was no overlying punctum. The clinical diagnosis was vascular malformation. He had no clinical signs or family
history of tuberous sclerosis complex (TSC), including renal angiomyolipoma, hypopigmented macules, facial angiofibromas or shagreen patches.

It had been treated with cryotherapy at the plastic surgery unit, but without any response. The patient himself had also been using home treatments, without any significant success.

An ultrasound examination showed a well rounded fibrofatty lump measuring 11 x 8 x 8mm. It did not show any flow on colour duplex and did not contain any dilated channels and the possibility of a vascular malformation was obviated. At this point, there was a clinical suspicion of skin cancer.

Under local anaesthesia, a 2cm oval piece of skin overlying the nodule was excised.

**Pathological findings**

Histopathological evaluation of the gross specimen revealed a 10mm fibrofatty nodule with normal overlying skin. The cut surface was yellow-white.

Light microscopic examination revealed a poorly circumscribed tumour with a poorly developed fibrous pseudocapsule (Figure 1a). The tumour was located mainly in the mid to deep dermis and subcutis, impinging onto the underlying skeletal muscle with focal extension into the superficial dermis. It was composed predominantly of mature adipose tissue, along with some intermingled blood vessels and smooth muscle bundles (Figure 1b). Adipose tissue was represented by variable sized groups of uniform lipocytes. Blood vessels were of varying size and shape (Figure 1c). Arterioles were rounded and had a thick muscular coat, while others were thin walled and slit-like resembling venules (Figure 1d). Occasionally, the vessels were engorged with red blood cells, but no thrombi were identifiable. Smooth muscle was arranged as narrow fascicles and small groups of cells dispersed among adipose tissue and blood vessels. Cytological atypia and significant mitotic activity were not seen; nor were areas of haemorrhage or necrosis. The histopathological diagnosis on H&E was AML.

In Masson’s trichrome (light green) stained sections, muscle bundles stained red and collagen green (figure 3). Sections stained with orcein and EVG for demonstration of elastic tissue revealed curved and partly formed elastic laminae in some of the thick walled vessels. EVG stained small arterioles within the lesion. Most of the vessels did not have elastic laminae.

The smooth muscle component showed cytoplasmic immunoreactivity for SMA (Figure 2a). Desmin staining showed focal immunoreactivity in the lesion (Figure 2d). The endothelial cell lining of the vascular spaces was strongly positive for CD31. S100 staining revealed no neural elements within the lesion. HMB-45 and Melan A immunoreactivity was absent (Figure 2b & 2c).

Based on these histologic and immunohistochemical features, a diagnosis of cutaneous AML was made.
**Discussion**

To our knowledge, only 21 cases have been reported in the English language literature. ²

Most AMLs are located in the kidney, but they have also been described in the liver, spleen and head and neck area. ⁵ Cutaneous AML is rare, occurs more commonly in men and presents as a solitary, painless nodule that is usually mistaken for a lipoma or cyst. ⁶ Most of the previously described cases have been on the acral skin or on the ear. ⁷, ⁸ They are usually 1 to 4 cm well circumscribed subcutaneous nodules. ⁹ The patient age has ranged from 16 to 77 years ⁹ with a reported median age on excision being 48.4 years, ¹ and a male: female ratio of 16:5. ¹

The most common clinical diagnoses were lipoma, vascular tumour and epidermal cysts. ¹, ¹⁰ Most lesions in the previous reports were described as ‘easily shelled out’, firm and encapsulated nodules without a frank epidermal connection. Signs of TSC were absent in all the reported cases. ¹ Although no recurrences have been reported in most of the cases, ⁶, ¹⁰, ¹¹, ¹² Büyükbabani et al experienced a patient with two previous local recurrences which seemed to be a result of incomplete surgical excision, ¹³ implying that simple complete excision is generally adequate treatment for a cutaneous AML.

Certain differences have been described between cutaneous and renal AML. ¹, ⁹ The renal form is often solitary (may be multiple in TSC-associated tumour), median age 46 years, shows a female predominance, TSC association in a third of cases, loss of heterozygosity (LOH) 9q34 and 16p13, smooth muscle cells showing diffuse marked cellular pleomorphism, immunoreactivity for HMB-45 and Melan A, present with abdominal and flank pain, haematuria, chills and fever. The cutaneous form is solitary, median age 50 years, shows a male predominance, no association with TSC, no LOH detected, smooth muscle cells are in fascicles with cigar shaped nuclei, no immunoreactivity for HMB-45 and Melan A, asymptomatic. ¹, ⁹ In contrast to renal AMLs, cutaneous AMLs are solitary, non-invasive and not associated with tuberous sclerosis and cured by simple surgical excision. ¹ In cutaneous AML, the smooth muscle is present as sheets and fascicles of spindled cells with cigar shaped nuclei. In contrast, the smooth muscle cells in renal AML generally appear to be less mature and are often present in a more diffuse pattern without the formation of distinct fascicles. ¹⁰ The smooth muscle cells in renal AML are not only immunoreactive for Desmin, but also unlike other smooth muscle tumours, express the melanoma-associated antigens HMB-45 and Melan A.

Since cutaneous and renal forms of AML have distinct clinical and pathological findings, Makino et al proposed the term ‘angiolipoleiomyoma’ for the cutaneous form. ⁹ Fitzpatrick et al also mention that although both terms are descriptive, they prefer the term cutaneous angiolipoleiomyoma to cutaneous AML for two reasons; firstly, they believe that it is most closely related to cutaneous angioleiomyoma and adding a descriptive syllable to acknowledge the lipomatous component is accurate from a descriptive standpoint and secondly, the use of the latter term may cause confusion with the renal AML, which is different both clinically and histologically. ¹⁰ Enzinger and Weiss stated that “the term ‘angiomylipoma’ should be reserved for a specific lesion arising most commonly in one or both kidneys as a solitary or multicentric mass.” ¹⁴
Cytological atypia and mitoses have not been observed in most cases, excepting one which presented marked pleomorphism in the smooth muscle component. Given that similar cytological changes have also been described in other benign tumours such as leiomyoma, schwannoma, pleomorphic lipoma and fibroma of tendon sheath, the author considered these changes to be degenerative, excluding the possibility of malignant potential as a result of pseudocapsulation without mitotic activity, no progression of the tumour for 15 years and no recurrence for 15 months after operation.

The tumour is said to derive from the smooth muscle cells of the venous wall. In the opinion of Büyükbabani et al, the large amount of adipose tissue, its dispersed appearance between vessels and smooth muscle bundles and the anomalous nature of the vascular component lacking elastic laminae account for the hamartomatous nature of the lesion and the unique features of this skin tumour qualify its individuation as a distinct entity separate from cutaneous angioleiomyoma. Although this was the traditional view, Okon and Dyduch remark that it is now well accepted that these lesions are clonal and neoplastic, like the other tumour-like lesions of tuberous sclerosis. They believe that the structural elements of AML, although recapitulating adipose tissue, vessels and smooth muscle have a different and common origin in the putative epithelioid perivascular cell (PEC). Obata et al conclude that since most cases of angiomylipoma were long standing lesions located at acral sites, and therefore exposed to external forces, some AMLs could be considered to be degenerated angioleiomyomas with replacement by fatty tissues. Makino et al regard AML to be a tumour of uncertain histogenesis.

Ashfaq et al have reported that smooth muscle cells in renal angiomylipoma react with HMB45, a monoclonal antibody raised against a melanoma cell line. They describe that the consistently reproducible pattern of HMB-45 immunoreactivity in renal angiomylipoma may be the result of a shared HMB-45 related antigen in the myoid component or renal angiomylipoma similar to that present in melanomas. They found that HMB-45 reactivity was absent in other smooth muscle tumours of the kidney, suggesting that the myoid cell of renal angiomylipoma may be unique. In line with other reports, we also found no staining for HMB-45. We conclude that HMB-45 reactivity is not a feature of smooth muscle cells in cutaneous angiomylipoma and that this is an unreliable criterion for its differentiation.

Angiolipoma, angioleiomyoma, piloleiomyoma, haemangioma with partial involution and fatty replacement, myolipoma and arteriovenous haemangioma are to be considered in the differential diagnosis. Confusion occurs only when the smooth muscle cells are not recognised and are mistaken for fibroblasts. Angiolipomas with fibrosis appear to be the tumour most likely to be confused with angiolipoleiomyoma. The large amount of smooth muscle and its location around the vessels permit easy differentiation from angiolipoma. A trichrome stain is the single most useful stain in differentiating AML from angiolipomas with increased fibrous tissue, wherein it would stain the fibrous tissue and smooth muscle differently. In piloleiomyoma, the tumour is composed of smooth muscle fascicles with indistinct borders and lacks a vascular component. Haemangiomas can exhibit partial involution and fatty replacement, however the presence of bundles of smooth muscle cells cannot be explained on this basis. Myolipoma of soft tissue usually occurs within the abdominal cavity and retroperitoneum. It represents a distinctive soft tissue tumour lacking...
medium sized vessels with thick muscular walls, such as those seen in AML. Arteriovenous haemangiomias may also occur in the subcutaneous tissues and demonstrate vascular spaces of both arterial and venous types associated with areas that resemble capillary or cavernous haemangioma. Arteriovenous haemangioma can be excluded because it is not circumscribed, lacks a fibrous pseudocapsule and lacks fascicles of smooth muscle intermixed with lipocytes. Subcutaneous cavernous haemangiomas may also occur, but the vascular spaces are larger, the vessel walls are thinner, the tissue surrounding the vessels lacks fascicles of smooth muscle and the tumour lacks a fibrous pseudocapsule. The histological differential diagnosis of cutaneous angiomyolipoma with pleomorphic changes includes pleomorphic lipoma. This was ruled out because of the absence of its typical floret like cells and because of the abundance of smooth muscle fibers. Moreover, pleomorphic lipoma is known to occur at the nape of neck and shoulder area. In our case, the intense and diffuse positivity for SMA differentiates it from ‘ancient’ schwannoma and from pleomorphic fibroma of tendon sheath. Finally, the abundance of adipose tissue and blood vessels easily differentiate it from pleomorphic leiomyoma.

The absence of mitotic activity, the pseudo-capsulation and the prolonged duration would support the benign nature of the lesion in our patient. These observations suggest that simple excision is generally adequate treatment for cutaneous AML.

This is the first reported case of AML in the lip and is unusual by the lack of circumscription. Unlike other authors, we did not note an increase in mast cells in the stroma of the lesion. Unlike Val-Bernal and Mira, we did not find lymphoid aggregates. 8

Cutaneous AML is an uncommon, distinct and likely under-represented tumour that should be considered in the differential diagnosis for a painless, slow growing, firm, subcutaneous nodule with a combination of blood vessels, smooth muscle cells and adipose tissue. These lesions are easily excised and do not recur on complete excision. At this time, there is no reason to proceed with an aggressive work-up for tuberous sclerosis in patients with a cutaneous AML as all 21 reported cases have displayed neither suspicious stigmata nor progression towards tuberous sclerosis. 3

**Conclusion**

Angiomyolipomas (AML) are rare benign mesenchymal tumours of either hamartomatous or mesenchymal origin, typically occurring within the kidney. We describe a case of AML presenting on the lip of an 85 year old male, which, to the best of our knowledge, is the 22nd case of cutaneous AML reported in the English literature. As the name suggests, it was composed of a mixture of mature adipose tissue, blood vessels and smooth muscle bundles. This is the first reported case of AML in the lip and is unusual by the lack of circumscription. The typical morphological features, special staining characteristics and immunohistochemical features help in exclusion of other differential diagnostic entities. As with all previously described cases, our patient did not present with the stigmata of tuberous sclerosis. AML should be considered within the differential for subcutaneous nodules and work-up for tuberous sclerosis should not be pursued when presenting in the skin.
Figure Legends

Figure 1a: Haematoxylin and Eosin staining of poorly circumscribed tumour x25

Figure 1b: Haematoxylin and Eosin staining showing adipose tissue, blood vessels and smooth muscle bundles in varying proportion x25

Figure 1c: Haematoxylin and Eosin staining showing convoluted vessels x25

Figure 1d: Haematoxylin and Eosin staining showing blood vessels of varying calibre x50

Figure 2a: Immunohistochemistry highlights positivity for SMA in the smooth muscle component x100

Figure 2b: Immunohistochemistry highlights focal positivity for Desmin in the smooth muscle component x100

Figure 2c: Immunohistochemistry shows no staining for HMB-45 in the tumour x100

Figure 2d: Immunohistochemistry shows no staining for Melan A in the tumour x100

Figure 3: Masson's trichrome stain showing predominantly collagen fibres stained green with occasional muscle fibres stained red x 200
References


7. Sánchez-Estella J, Bordel-Gómez MT, Zamora-Martínez T. Presentation of 2 new cases of cutaneous angiomyolipomas and literature review. Actas Dermosifiliogr 2009; 100: 808


15. Okoń K, Dyduch G. To the editor: Is this cutaneous angiomyolipoma truly an angiomyolipoma? Indian Dermatology online Journal 2013; 4(1): 65

Figure 2: Final Fig 2.tif
Figure 3: Final Fig 3.tif