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Clinical Quiz

Dedifferentiation of an atypical lipomatous tumor of the thigh - a 6 year follow-up study

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Case

A 69 year old male, presented elsewhere 6 years earlier with an undiagnosed mass of the left femoral triangle. MRI was performed and showed a big tumour consistent with an atypical lipomatous tumour/well-differentiated liposarcoma. The patient had non-significant past medical history, was a non-smoker, normal weight male (BMI: 23) with negative family history for malignant diseases and lived in a rural area. He was advised to proceed with tumour resection; however, the patient left the mass untreated and unattended. When he came to our clinic six years later, he reported pain in the cranial base and the cervical spine, without neurological symptoms. On the left thigh area he had a significant painless palpable mass. Imaging tests were performed; MRI showed significant increase in the known mass (new dimensions 20x15x28cm) with transformation and atypical features such as calcified areas (Figure 1). CT scan on the cervical and thoracic area showed an osteolytic bone metastasis on the clivus of the skull and on the C2 and C4 vertebrae. There were no signs of metastasis of the lungs (thorax CT). The x-ray on the left thigh area showed healthy femoral bone and many calcified foci areas of various dimensions, from 2 cm to 0.3 mm, mostly in the medial aspect of the tumour.

A trucut biopsy was performed; the histological findings were consistent with a high grade (III) spindle cell sarcoma with focal nuclear atypia, high mitotic activity and extended necrotic areas expressing smooth muscle differentiation markers in immunohistochemistry [Vim(+), S100(-), SMA(+), Desmin(+), Calponin(+), MDM2(-), CDK4(-)] (Figure 2).

He was referred to the multidisciplinary tumour board of our centre, where a palliative approach was adopted; the patient succumbed to his disease few weeks later.

Discussion

ALT/WDL accounts for about 40% to 45% of all liposarcomas and they represent the larger subgroup of adipocytic malignancies. They are usually diagnosed after the fifth decade of life with a slight predominance in males[1,2]. Atypical lipomatous tumours/Well-differentiated liposarcoma are used as equivalent terms but there has been a controversy over the terminology of such tumours. It has been proposed that the term well-differentiated liposarcomas could be used for retroperitoneal/mediastinal tumours where wide excision is usually impossible and dedifferentiation more probable and therefore they have more aggressive course. On the other hand when these tumours are seated in the extremities or trunk complete excision is frequently possible making the prognosis more favourable and hence they are termed atypical lipomatous tumors[3]. Histologically ALT/WDL consist of mature adipocytic cells separated by collagen septae, with scattered atypical stromal cells and variable amount of multivacuolated lipoblasts[1]. Fibrous and myxoid tissue is very limited but still consistent with this diagnosis. When cellular myxoid and fibrous areas are present in notable portions this is considered to be a sign of low-grade dedifferentiation from the beginning[3]. Positivity in overexpression of MDM2, HMGA2 and CDK4 it is considered to be a reliable hallmark by some authors in order to distinguish those tumours from pure intramuscular lipomas. Other karyotype aberrations such as ring chromosomes and/ or giant chromosomes may aid the diagnosis[1].

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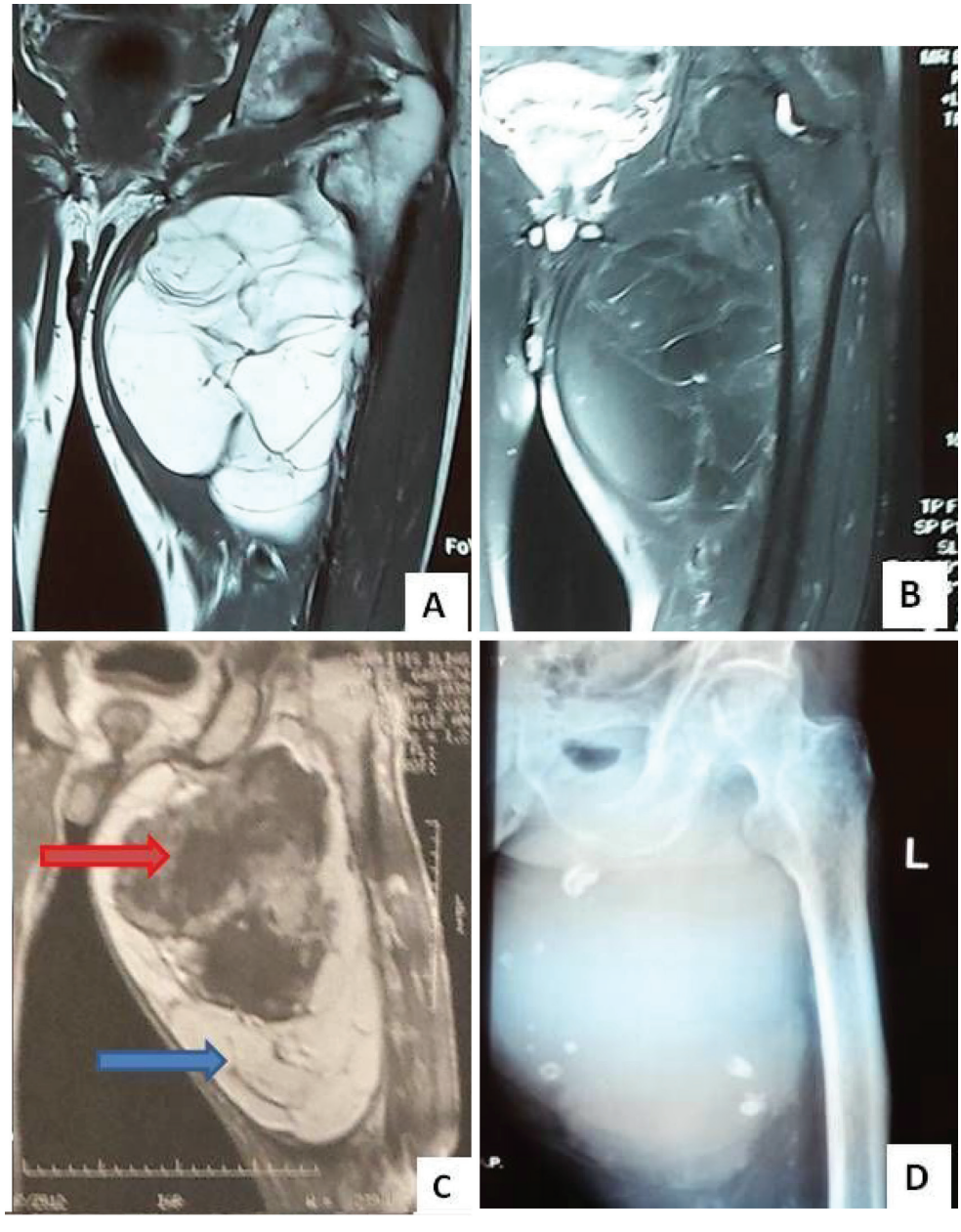

Figure 1. **A:** Coronal MRI (T1 sequence) shows a homogeneous fatty tumor with septation compatible with ALT/WDL. **B:** Coronal MRI (T1 with fat suppression): the whole fatty tumor except from the fibrous septa is suppressed. **C:** Coronal MRI (same sequence) 6 years later: the tumor has grown in size and has dedifferentiated, as depicted by the arrows: blue arrow shows the same fatty component, however red arrow shows the dedifferentiared area of the tumor, consistent with a high grade sarcoma. **D:** xray of the thigh showing many calicified foci within the tumor, consistent with the dedifferentiated areas. The femoral bone is not involved.

ALT/WDL almost never metastasize unless they undergo dedifferentiation, only exceptional though in extremity tumors[2-5]. The risk of dedifferentiation in a recent metanalysis was around 1% in extremity tumors, whereas it was much higher in retroperitoneal (17%) or groin lesions (28%) (Rauh et al, BMC 2018). On the other hand, local relapse is frequently reported from as low as 7% to as high as 43% in some early series[2-5]. Marginal excision (even shelling out of the tumour) usually suffices for adequate local control. Unless gross tumour is left behind, recurrence in experienced centres is less than 10%[1,2,5]. Adjuvant Radiation therapy seems to have little role in the therapeutic algorithm[1,2] since the prognosis is generally favourable and it may potentiate dedifferentiation[5]. Some authorities advocate long term surveillance since

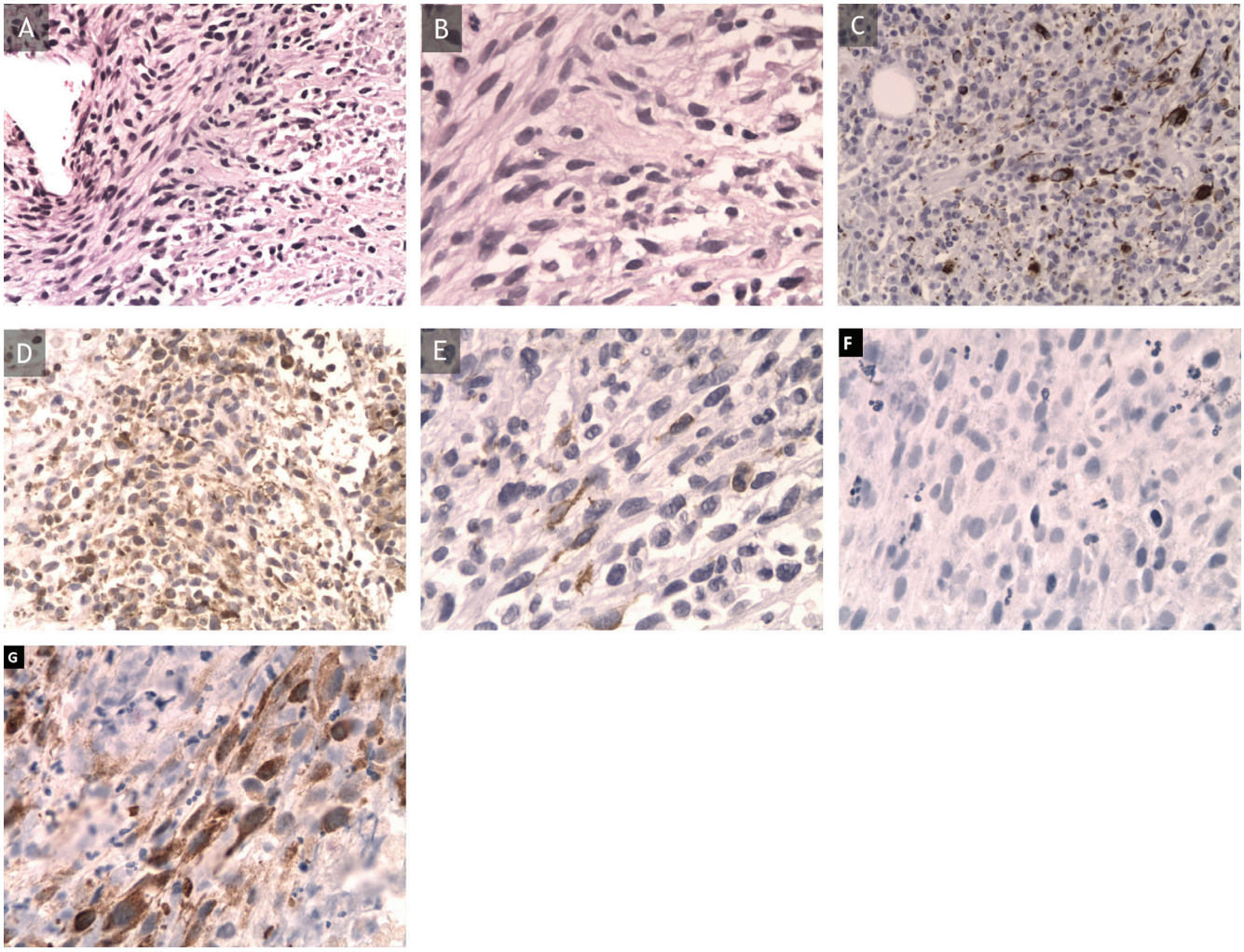

Figure 2. A: Hematoxylin and Eosin (H&E) staining x 200 (magnification) showing malignant mesenchymal spindle cells with mitotic activity on the left side of the slide, adjacent with necrotic area on the right side, compatible with high grade sarcoma. **B:** H&E x 400 (higher power magnification) better depicting the mitotic activity and atypical nuclei. **C:** Immunohistochemistry (IHC) analysis x 200 showing focal intensive with desmine. **D:** IHC x 200 diffuse positivity for Calponine and **E:** IHC X 400, focal expression of SMA. **F:** Negative expression for MDM2 (IHC X 400) and **G:** no nuclear expression for CDK4 (IHC X 400) (although positive in the cytoplasm).

recurrences have been noted even 12 years postoperatively[2] whereas others do not[1]. In our practise we generally follow up the patient with MRI in a yearly basis for the first 5 years and then less frequently until 10 years after surgery. Of course the patient is advised to check the affected area on a monthly basis and if new lumps or "swelling" is noticed he/she should return immediately in the clinic.

Although the behaviour of well-differentiated liposarcomas is strongly influenced by location, this case report indicates that dedifferentiation is not only a site-specific phenomenon, but is also a time-dependent phenomenon especially if left untreated for a long period of time[3]. In such cases close surveillance should be advocated and if the tumour grows or changes pattern, immediate surgery should be undertaken.

In conclusion, ALT/WDL represent the larger subgroup of adipocytic malignancies. If left untreated for long time period, even in the extremities, it may be transformed in high grade sarcoma with a dismal prognosis. Instead, marginal excision is usually curative.

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Questions

1. Are the terms intramuscular lipomas, atypical lipomatus tumor (ALT) and well differentiated liposarcomas (WDL) synonyms?
A. Yes
B. No
C. No but they hold similar features

Critique

All three entities refer to deep seated benign fatty tumors. However, ALT/ WDL hold some atypical histological features (scattered lipoblasts, variable size vacuoles, atypical stromal cells, overexpression of MDM2, HMGA2 and CDK4). ALT refers more to extremity/ trunk adipocytic tumors where complete excision is usually possible and prognosis is more favourable, whereas WDL in retroperitoneal cases where wide excision is frequently not possible and relapse or dedifferentiation of the tumor more probable.
The correct answer is C.

2. What is the optimal treatment of ALT/WDL?
A. Wide excision plus plus Radiation Therapy (RT)
B. Marginal excision (shelling out of the tumor) plus RT
C. RT alone
D. Marginal excision alone

Critique

Marginal excision suffices for adequate local control. There is little role for RT in these benign tumors plus it may potentiate dedifferentiation.
The correct answer is D.

3. What is the prognosis after marginal excision in ALT?
A. Local relapse (LR) around 40% and no metastasis.
B. LR around 10% and no metastasis.
C. LR 40% and 5% metastasis
D. LR 10% and 10% metastasis

Critique

Although LR has been reported up to 43% in pure ALT series (not including WDL) in experienced centres the relapse is no more than 10%. As mentioned before, these benign tumors do not metastasize.
The correct answer is B.

4. Since ALT hold benign features can they be left alone?
A. Yes
B. Yes but with surveillance
C. No

Critique

Although they do hold benign features and do not metastasize, if left alone for long time periods they may dedifferentiate in higher grade sarcomas with dismal outcome, as outlined in the case report. Therefore, marginal excision is advised; however, if nonoperative treatment is fostered, these tumors should be followed with serial MRIs and if they grow or change in consistency they should be excised immediately.
The correct answer is B.