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Case Report

Malignant granular cell tumour of the thigh with lung metastases in a young woman; a rare presentation

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Abstract

Granular Cell Tumour (GCT) is an uncommon soft tissue neoplasm. Majority of GCT are benign involving the soft tissue of the head and neck region. However, few show malignant behaviour with local recurrence and distant metastases often involving the lower extremities. Here we report a rare case of malignant granular cell tumour in a 33-year-old woman involving the left thigh with regional lymph node and multiple lung metastases.

Introduction

Granular Cell Tumour (GCT) is a rare soft tissue neoplasm, accounting for 0.5% of all soft tissue neoplasms and was first described by Alexei I Abrikossoff, a Russian pathologist in 1926 [1]. This tumour was originally described as 'granular cell myoblastoma' as the origin was thought to from skeletal muscle. Recent studies show that it is more likely to be of neural in origin [1,2]. GCT commonly affects women in the third to fifth decades and shows predilection for patients of Afro-Caribbean origin. It is rare in children. GCT often presents as a slow growing painless nodule, commonly involving the head and neck region with highest predilection for tongue but can occur in any anatomical location [1].

The majority of GCT pursue a benign course with less than 2% showing malignant behaviour. The diagnosis of Malignant GCT is based on evaluation of clinical and radiological findings, and assessment of histological features.

Malignant GCT (MGCT) most commonly affects patients in their 4^{th} –5^{th} decade of life and unlike its benign counterpart which often involves the head and neck region, typically occurs in lower extremities. However, both benign and malignant GCT, have been found in a wide variety of other locations, including skin, heart, lung, abdominal wall, etc. [3]. Characteristic histological appearance of GCT is the presence of large polygonal cells with finely granular, abundant, eosinophilic cytoplasm. If a malignant lesion is suspected based on clinical and imaging findings and histology reveals a GCT, further assessment of histomorphological criteria proposed by Fanburg Smith et al., is recommended. Six morphological criteria for diagnosis of malignant GCT as suggested by this group include spindling of tumour cells, increased nuclear to cytoplasmic ratio, nuclear pleomorphism, necrosis, vesicular nuclei with large nucleoli and increased mitotic activity (>2 mitoses per 10 high-powered fields). GCT that meets three or more of these criteria are classified as malignant, whereas tumours showing one or two criteria are classified as atypical while benign ones display only focal pleomorphism if any [3,4].

Local recurrence and metastasis are significantly high in MGCT, with a 32 % of recurrence rate and metastases in 50 %. The most common metastatic sites are regional lymph nodes, lungs and bones [5,6]. It has been established that older age group, larger tumour size, local recurrence, metastasis, mitotic index of >10%, and p53 immunoreactivity are all adverse prognostic factors [6].

Compared to their benign counterpart MGCT tend to have longer clinical presentation with sudden rapid growth, they are larger in size at presentation, and usually have a history of local recurrence. Treating MGCT is

challenging. Wide local excision is generally the main stay of treatment. Chemotherapy and radiotherapy are not shown to have significant impact over the clinical course of the disease [5]

Benign GCT has excellent outcome following surgical resection. Thus, differentiating a malignant from benign GCT is important as malignant GCT has an aggressive course and poor prognosis with a mortality rate of 40%.

Case report

A 33-year-old, previously healthy woman presented with a painless left thigh lump for 6 months, which was rapidly enlarging for the last 2 weeks. There was no associated pain or changes of the overlying skin. She did not have weakness or abnormal sensation of the limb or history of loss of appetite or weight.

On examination, the left thigh lump was firm, well defined with limited mobility and around 80 mm in maximum diameter. It was not attached to the skin and regional lymph nodes were not enlarged.

The Contrast-Enhanced Computed Tomography (CECT) of the pelvis and lower limbs showed a large heterogeneously contrast enhancing mass lesion measuring 88x70x50mm in the left thigh (Figure 1A), arising from the adductor compartment. Low density non enhancing areas within the lesion (Figure 1B) due to necrosis were noted. There were no calcifications, infiltration of the overlying skin or subcutaneous tissue or changes in underlying left femur. Multiple enhancing lymph node masses in the left inguinal region and large intrapelvic lymph nodes along the left internal iliac vein measuring 44mmx46mm and two lytic lesions measuring 12x15mm and 8x5mm in the body of 5th lumbar (L5) vertebra were also evident. Features were consistent with a large soft tissue sarcoma of the left adductor muscle with lymph node and bone metastasis. The Chest X -Ray (CXR) showed multiple metastatic deposits in bilateral lung fields (Figure 1C).

Tru cut biopsy of the thigh lump comprised of four fragments altogether measuring 5.5x0.2x0.2cm. Microscopy revealed a lesion composed of nests and sheet (Figure 2A) of

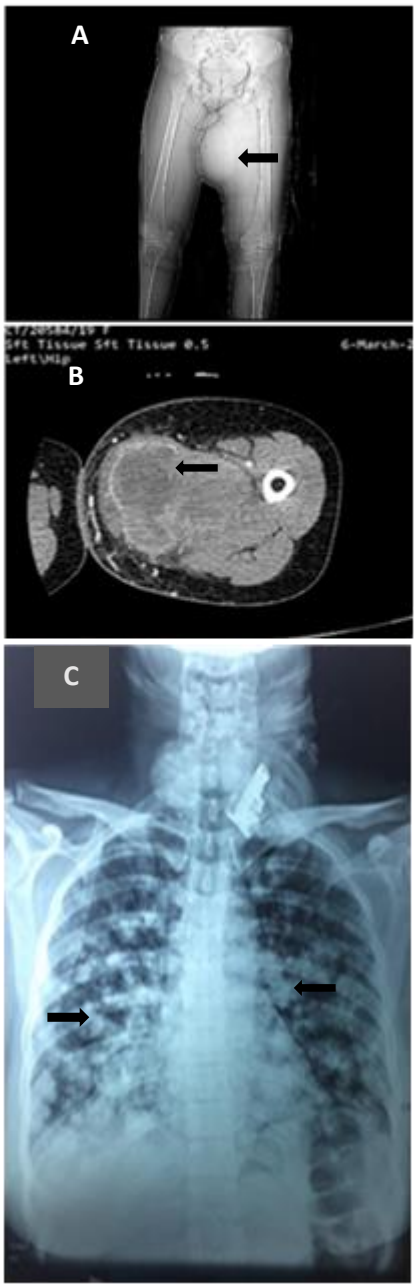

Figure 1: *CECT pelvis and lower limb A - Large heterogeneously contrast enhancing mass lesion at the adductor compartment (arrow). B - Contrast enhancing mass lesion with a non-enhancing area within the lesion (arrow). C – CXR shows multiple metastatic deposits in the lung(arrows)*

polygonal cells with abundant granular eosinophilic cytoplasm. (Figure 2B) Nuclei were enlarged vesicular with fine chromatin and conspicuous nucleoli. Mitoses or necrotic foci were not seen. These features were compatible with a granular cell tumour. Tumour cells were strongly and diffusely

positive with S 100. (Figure 2C) They were negative for Desmin and MyoD1. The Ki67 index was around 40% (Figure 2D). Based on imaging and the histology the diagnosis of malignant granular cell tumour was made.

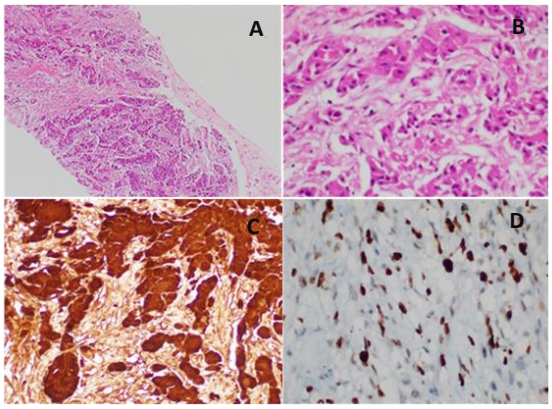

Figure 2: *A - Biopsy with a tumour arranged in nests and sheet of polygonal cells (H&Ex100). B- Polygonal cells containing round to oval enlarged nuclei with vesicular chromatin and conspicuous nucleoli and abundant granular eosinophilic cytoplasm (arrow) (H &E x400). C - S100 shows diffuse nuclear and cytoplasmic positivity in tumour cells(x400). D- Ki67 shows 40% proliferative index (x400).*

Wide local excision of the thigh mass was performed as it is the main stay of treatment and also for further evaluation of histological criteria for malignancy. The specimen comprises a mass of tissue measuring 80x60x60mm. Cut surface showed areas whitish and tan in colour (Figure 3A).

Microscopic examination of the mass revealed a tumour composed of large polygonal cells with eosinophilic granular cytoplasm. Cells were arranged as ribbons and nests divided by fibrous connective tissue. (Figure 3B) Nuclei were vesicular with moderate pleomorphism and displayed prominent nucleoli (Figure 3 C &D). Mitoses were noted (Figure 3C) and Mitotic count was 4/10 HPF. There were no areas of necrosis. The tumour was within 1mm of the resection margin. (Figure 3B).

As 4 histological criteria described by Fanburg Smith were met, the final diagnosis of MGCT was confirmed based on clinical history, examination and imaging findings including presence of lung metastases.

Discussion

MGCT is an exceedingly rare and aggressive tumour, representing less than 1 - 2% of all GCT and 0.2% of all soft tissue sarcomas [6].

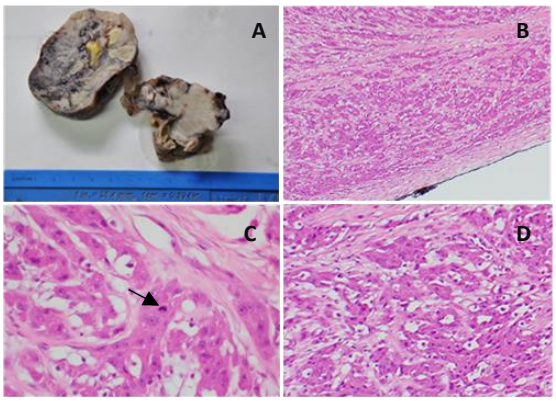

Figure 3: *A – Wide local excision of the thigh mass composed of mass of tissue measuring 80x60x60mm and cut section with whitish and tan in color. B- Tumour cells were arranged as ribbons and nests divided by fibrous connective tissue. The tumour focally lies within 1mm of the resection margin(arrow) (H&Ex100) C- Nuclei were vesicular and showed moderate pleomorphism and display prominent nucleoli. Mitotic figure was noted(arrow) (H&Ex400). D- Nests of polygonal tumour cells with abundant eosinophilic cytoplasm.*

The commonest sites involved are extremities and trunk. In 1998, Fanburg Smith et al. established the criteria for diagnosing benign, atypical, and malignant granular cell tumours based on histological features as highlighted in the introduction above. However, presence of metastases is the only definite criteria for malignancy for GCT [1,5,6].

This patient shows 4 of the above histological criteria set by Fanburg Smith et al., namely, 4 mitoses/ 10 HPF, nuclear pleomorphism, vesicular nuclei with prominent nucleoli and high nuclear cytoplasmic ratio. Also, the presence of metastatic deposits in lungs was confirmatory of MGCT.

The histological differential diagnosis of MGCT include rhabdomyosarcoma, leiomyoma, leiomyosarcoma with granular cell change, alveolar soft part sarcoma, hibernoma and epithelioid sarcoma. Rhabdomyosarcomas are also composed of polygonal rhabdomyoblasts that express muscle markers. In contrast GCT is positive for S-100 protein and negative for desmin and myogenin. Leiomyoma and

leiomyosarcoma with granular cell change are positive for muscle markers and negative for S-100. Alveolar soft part sarcoma which also shows positivity for S-100 displays an alveolar pattern of arrangement of tumour cells in contrast to the sheets like arrangement in GCT. Hibernomas have vacuolated cytoplasm unlike granular cell tumour. Epithelioid sarcoma displays a background of necrosis and inflammatory cells with positivity for epithelial markers such as cytokeratins and Epithelial Membrane Antigen [1,2].

The clinical information and radiological findings are mandatory for the diagnosis of a MGCT.

MGCTs have a poor prognosis with 32% local recurrence and 50% metastatic rate [5,6]. It can metastasize up to several years following the initial surgical excision. Common metastatic sites for MGCT are lymph nodes, lungs, liver, and bones. [7,8]. Poor prognostic factors associated with MGCT are older patient age, large tumor size, increased mitotic activity and Ki-67 index greater than 10%. In this patient, the only favorable prognostic factor was younger age. Benign and atypical GCT have favourable outcome with no susceptibility for metastasis. MGCT has 39% mortality rate in 3-year interval [5,6]. The treatment of choice is complete surgical resection with clear margins and regional lymph node dissection [4]. The tumour is resistant to radiotherapy. This patient was started on chemotherapy and planned for regular follow up at the oncology clinic.

Conclusion

Diagnostic criteria of malignancy in GCT are debatable. The presence of metastases is currently considered as the only unequivocal indicator of true malignancy. Complete surgical resection of the tumour with clear margins, regional lymph node dissection and chemotherapy for distant metastases are the available treatment modalities. Although surgical resection was performed in this patient the tumour resection margin clearance was less than 1mm. As she has lung metastases chemotherapy has been offered.

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