Case Report: Cutaneous granular cell tumors [version 1; peer review: 2 approved with reservations]

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Abstract
Granular cell tumors are uncommon tumors in the deep soft tissue of the extremities, especially those with intramuscular origin, with a good prognosis after surgical resection. We present a case study of a 30 year old man with a skin lesion on his shoulder, which was grown in size over the course of 2 months. Complete tumor excision was done and histopathological findings revealed a marked hyperplasia epidermis with pseudoepitheliomatous pattern. The pathologic report was compatible with a granular cell tumor.

Keywords
Granular cell tumor, skin, atypical type

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Introduction
Granular cell tumor (GrCT) is a benign tumor of the nerve sheath, which more commonly occurs in the tongue, breast, skin and subcutis. It can affect the dermis, subcutis or submucosa. Granular cell tumors are uncommon tumors and most of them have a good prognosis after surgical resection, however, around 0.5–2% of these tumors may be malignant, which have a poor prognosis due to local recurrence and distant metastasis.1–3

Granular cell tumors are rare in the deep soft tissues of the extremities, especially those of intramuscular origin.2–5 Although this type of tumor is more common in the 4th to 6th decades of life, one study found that GrCT occurs more commonly between 30–40 years of age.1 In this case report, we present a 30 year old man with a skin lesion, which was diagnosed as a granular cell tumor.

Case report
A 30 year old man was referred to the pathology department of the Imam Hospital, Sari, Iran in August 2017, and presented with a skin lesion on his right shoulder (Figure 1). He had no pain or trauma, and no significant past medical history. The patient had the skin lesion for 6 months previous to presentation, which had grown slowly in size over the course of previous 2 months. The lesion size was approximately 2 cm in diameter with a verrucous appearance. On physical examination, a hard, fixed and non-tender skin mass was palpable on his right shoulder.

Complete tumor excision was performed and histopathological findings revealed a marked hyperplasia epidermis with pseudoepitheliomatous pattern (Figure 2A). The dermis showed ill-defined and diffuse proliferation of large round to oval cells, with brightly eosinophilic granular cytoplasm (Figure 2B). Mitotic activity was rare. Atypia and necrosis was not seen. The pathologic report was compatible with a granular cell tumor.

Immunohistochemical (IHC) staining was carried out for this patient in the pathology department of Imam Khomeini hospital. All samples were fixed in 10% buffered formalin and embedded in paraffin. Sections were cut 4 μM thick from wax blocks, mounted on to 3-Aminopropyltriethoxysilane (APES)-coated glass slides. Slides were deparaffinized in xylene twice for 10 minutes, rehydrated through graded ethanol to distilled water before incubation for 15 minutes with 3% hydrogen peroxide-methanol to inhibit endogenous peroxidase activity, and heated in 0.01 M citrate buffer (pH 6.0) in a microwave oven for 5 minutes at 100°C; after boiling for antigen retrieval. Then the slides were taken out of microwave oven and cooled to room temperature for 30 minutes. After incubating for 15 minutes in a blocking solution containing 10% normal goat serum in PBS, sections were incubated at 4°C overnight in a humidified chamber with CD68, S100, neuron specific enolase (NSE), vimentin, Ki67, desmin and SMA antibody.6 The prepared stained slides were read using Olympus CX31 microscope.

Periodic acid–Schiff stain (PAS) was positive in the suspected tumor cells, and IHC results showed, CD68 (Manufacturer No. Mob167, species: mouse, clone ID No: kp1, concentration: 1:100; CellPath Ltd, UK), S100 (Manufacturer no. Z 0311, species: rabbit, clone ID No: polyclonal, concentration: 1:500; Agilent, Santa Clara, CA, USA), NSE (Manufacturer no. RP 054, species: rabbit, concentration: 1:50; CellPath, UK), and vimentin (Manufacturer no. Mob 090, species: mouse, clone ID No: v9, concentration: 1:50; CellPath, UK), were strongly positive (dark brown staining +3) in suspected cells (Figure 3-A, B, C) and Ki67 (Manufacturer No. DB D-125, clone: C16-I, species: rabbit, concentration: 1:200; DB Biotech, Kosice, Slovakia) was positive in 3% of tumor cells. Desmin and SMA were negative (Figure 4- A, B). Finally, the granular cell tumor was confirmed and the patient has been followed for 1 year after the surgery and no recurrence has been reported.

Discussion
GrCT was first described in 1926 as a myoblastoma which arises from the muscle in the tongue. Apart from the tongue, the skin and soft tissues are other common locations for GrCTs.1 In 1935, Feyrter described the tumor as a granular cell neuroma because he hypothesized that the tumors were neural in origin. Fust and Custer named the tumor as granular cell neurofibroma in 1948. Finally in 1962, Fisher and Wechsler named the tumors as granular cell schwannomas, because Schwann cells was their most probable origin. Nowadays the name adopted by WHO is granular cell tumor.1 GrCT usually presents as a solitary and

Figure 1. photograph of skin lesion with verrucous appearance on patient’s right shoulder.
small nodule, as a painless mass. It is most common in women aged 30–60 years old\textsuperscript{1,2}. The presented case had a painless mass and as a 30 year old male, he did not conform to epidemiological evidence on the most common sex\textsuperscript{3}. Furthermore, based on the clinical findings, the dermatologist diagnosed this lesion as dermatofibroma and keratoacanthoma and no differential diagnosis had been reported. However, the pathology report showed different results and identified it as granular cell tumor.

To our knowledge, three similar cases of GrCT with distinguished dermatofibroma-like morphology have been described in the literature. However, all these cases were presented as atypical
GrCT. One was a 60 year old woman with a nodule on the back\(^5\), the second was a 48 year old man with a lesion in the pubic area\(^7\) and the third case was a 62 year old woman with a tumor on her back under the right scapula\(^8\).

According to 6 histological criteria, GrCT can be classified as benign, atypical or malignant. The criteria are necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high-power fields), high nuclear to cytoplasmic ratio, and pleomorphism\(^6\). Tumors with 1 or 2 of these criteria can be classified as atypical. Another classification system states the only difference between benign GrCT and GrCT-uncertain malignant potential is the presence of necrosis and/or mitoses\(^9\). As to the former classification system, there are some cases of histological mild atypical GrCTs, which presented a malignant clinical course such as local recurrence, rapid recent growth, and large tumor diameter\(^10\).

GrCTs are relatively uncommon and benign in most of the cases\(^1,11\). Malignant and atypical GrCTs account for only a small percentage of cases\(^7\). The most common immunological marker presented by GrCT is S100 protein. In our case, we excluded possible diagnosis of granular cell dermatofibroma (S100-protein negative) and malignant peripheral neural sheath tumor (weak S-100 expression). CD68, CD57, and NSE may be positive in GrCT cases\(^1\). We can evaluate malignant potential in GrCTs by the means of Ki-67 proliferation index. If the index is greater than 10% in a specific case, the malignant potential is higher in that case, although not all malignant GrCTs have a high Ki-67 index. In addition to immunological markers mentioned above, it is shown that 68% of GrCTs express p53 in over 50% of tumor cell nuclei\(^1\).

In conclusion, we presented a case of GrCT with the dermatofibroma-like morphology fulfilling criteria of benign GrCT and immunohistochemical positivity of S100, CD68, and NSE. The necessity for S-100 staining to differentiate granular cell tumor with dermatofibroma from dermatofibroma-like GrCT is highly recommended.

Informed consent
Written informed consent for the publication of the patient’s clinical details and images was obtained from the patient.

Data availability
Dataset 1: Raw microscope images 10.5256/f1000research.13015.d207010\(^16\)

Competing interests
No competing interests were disclosed.

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References

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Jeffrey M Farma
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This is a case report on Cutaneous granular cell tumors.
  ○ They should remove that they occur on the extremities as their case is actually on the truncal region.
  ○ Why did they include how the slides were processed? This is useless information.
  ○ The only novel part of this is the dermatofibroma-like morphology but overall I do not feel this case report adds much to the literature.
  ○ What margins did they take on the excision?
  ○ How long was the followup on the patient?

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical oncology, DFSP, granular cell tumors, melanoma, sarcoma, squamous cell carcinoma, merkel cell carcinoma, colon cancer, rectal cancer, gastric cancer,
neuroendocrine tumors.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 October 2018

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Nikoo Mozafari
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A case of granular cell tumor, with usual and typical presentation has been described. The manuscript needs English editing.

**Introduction:**
The importance or novelty of this case has not been clarified.

**Case report:**
Why was patient referred to pathology department?
Explaining method of IHC, is unnecessary.
Figure 4a and figure 4b are identical, but authors have mentioned that these are 2 different slides stained with 2 markers.
The quality of photos are not acceptable, photos with higher resolution are required.

**Discussion:**
More explanation about “granular cell dermatofibroma” and methods of its differentiation from “granular cell tumor” seems necessary.
A lot of IHC markers (such as CD68, CD57, and NSE) have been used but no data on their utilities have been given. How can these markers be helpful in differentiating “granular cell tumor” from other entities?
This term seems to be wrong: “granular cell tumor with dermatofibroma”

**Is the background of the case's history and progression described in sufficient detail?**
Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Yes
Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
No

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

**Competing Interests:** No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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