Typical and Atypical Granular Cell Tumors of Soft Tissue

A Clinicopathologic Study of 50 Patients

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ABSTRACT

Objectives: *Granular cell tumors are rare neoplasms of neural origin. Despite the mesenchymal nature of these tumors, they rarely occur in the soft tissue, and as a result, this subset is not well characterized. We present the largest case series to date comprising 50 patients with benign and atypical soft tissue granular cell tumors in an effort to better define the pathologic features in this subset of lesions.*

Methods: *All cases of soft tissue granular cell tumors from the Ohio State Medical Center and the Medical College of Wisconsin over a 10-year period were reviewed for histologic and clinical findings.*

Results: *The most common location was the upper extremity. The mean age was 38.6 years, and the mean size of the tumor was 2.1 cm. An infiltrative growth pattern was seen in 58.8% of cases, and positive margins were found in 68.2%. Eleven (21.6%) cases showed evidence of cytologic atypia and fulfilled the criteria for a diagnosis of atypical giant cell tumor. Two of 11 patients with long-term follow-up experienced local recurrence.*

Conclusions: *Compared with granular cell tumors overall, the soft tissue subset shows a larger average size and higher propensity for incomplete resections, with atypical features being relatively common. Our findings suggest that soft tissue granular cell tumors may be slightly more aggressive than their dermal or organ-confined counterparts.*

Granular cell tumors (GCTs) are rare lesions believed to be of neural origin.[1,2] They can occur in almost any location along mucosal surfaces, including the tongue, within organs, or within the dermis or subcutis.[1,3,4] These tumors are typically benign, although they are often infiltrative and can recur.[5] GCTs can be malignant, although this is somewhat rare and seen in less than 2% of GCTs.[6]

GCTs of the soft tissue are rare and not well characterized, representing only 0.5% of all soft tissue tumors.[7] Most of the literature on GCTs of soft tissue comes from case reports or small case series.[5] We present a series of 50 patients with 51 cases of GCTs of soft tissue to provide further characterization of this subset of GCTs.

Materials and Methods

The electronic files of the Ohio State Medical Center Department of Pathology and the Medical College of Wisconsin Department of Pathology were examined for cases of GCT, and only those that occurred exclusively in soft tissue were included in this study. We define soft tissue GCTs as those exclusively involving subcutaneous or intramuscular tissue without involvement of skin or other organs. Data extracted from the patient's electronic medical record and pathology reports, including age, sex, location, size of the lesion, histopathologic features, and clinical follow-up (when available), were collected.

For histopathologic examination, histologic glass slides stained with H&E were reviewed. A total of one to six H&E glass slides (mean, three slides) were available

Table 1
Clinical and Histologic Features[a]

Patient No.	Age, y	Sex	Location	Size, cm	Depth	Infiltrative	Atypia	Margins
1	52	F	Flank	1	SC	No	Benign	NA
2	43	M	Arm	1.4	SC	Focal	Benign	Positive
3	35	M	Axilla	1.2	SC	Yes	Benign	NA
4	29	F	Axilla	1.5	SC	No	Benign	NA
5	32	F	Arm	2	IM	Yes	Benign	NA
6	45	F	Arm	2	SC	No	Benign	NA
7	69	F	Chest	2	IM	Yes	Benign	Negative
8	29	M	Chest	3.5	SC	Yes	Benign	NA
9	60	M	Chest	1.8	SC	Focal	Benign	NA
10	40	F	Chest	2	IM	Focal	Benign	Negative
11	41	F	Chest	2	SC	Yes	Benign	NA
12	5	M	Foot	1.5	SC	Yes	Benign	Positive
13	13	F	Scalp	2.5	SC	No	Benign	Positive
14	11	M	Scalp	1.3	SC	No	Benign	Positive
15	48	F	Axilla	3	SC	Yes	Benign	NA
16	35	F	Vulva	2	SC	No	Benign	NA
17	43	F	Hand	2.5	SC	Yes	Benign	NA
18	47	F	Hand	3	SC	No	Benign	NA
19	50	M	Hand	3.5	SC	No	Benign	NA
20	23	M	Back	2.3	SC	Yes	Benign	Positive
21	28	M	Hand	2.5	SC	No	Benign	NA
22	45	F	Foot	3.3	SC	Yes	Benign	Positive
23	19	M	Chest	2.5	SC	Focal	Benign	NA
24	37	F	Finger	1.3	SC	No	Benign	NA
25	6	F	Leg	0.7	SC	Yes	Benign	NA
26	52	F	Leg	2.5	SC	Yes	Benign	NA
27	48	F	Thigh	1.5	IM	Yes	Benign	NA
28	45	F	Axilla	0.6	SC	Focal	Benign	Negative
29	53	F	Back	1.2	SC	Yes	Benign	Positive
30	61	F	Thigh	3.6	SC	Yes	Benign	Negative
31	37	F	Finger	0.5	SC	No	Benign	NA
32	43	F	Buttock	1	SC	Yes	Benign	Positive
33	22	F	Chest	0.2	SC	Yes	Benign	Positive
34	44	M	Forearm	0.6	SC	No	Benign	Negative
35	44	M	Back	8	SC	Yes	Benign	NA
36	56	F	Flank	1.5	SC	No	Benign	Positive
37	49	F	Vulva	2	SC	Yes	Benign	Positive
38	46	F	Wrist	2.0	SC	Yes	Benign	NA
39a	26	F	Thigh	1.7	SC	Focal	Benign	Positive
39b	26	F	Buttock	3	SC	Yes	Benign	Positive
40	35	M	Arm	3	SC	No	Atypical	NA
41	67	M	Arm	2	SC	No	Atypical	Negative
42	55	F	Arm	2	SC	Focal	Atypical	Positive
43	22	F	Chest wall	2.2	IM	No	Atypical	NA
44	14	F	Leg	2.3	SC	No	Atypical	NA
45	10	M	Cheek	1.9	SC	No	Atypical	NA
46	45	F	Hand	2	SC	No	Atypical	NA
47	47	M	Thumb	0.8	SC	No	Atypical	NA
48	44	F	Foot	4.8	IM	Yes	Atypical	NA
49	23	M	Cheek	0.9	SC	Yes	Atypical	Positive
50	57	M	Flank	1.8	IM	No	Atypical	Negative

IM, intramuscular; NA, not available; SC, subcutaneous.
[a]Patient 39 had two separate but simultaneous tumors.

for review from each lesion. Immunohistochemical stains for S-100 protein were performed in all cases to support the diagnosis using standard immunohistochemical techniques. Follow-up information was obtained from the medical records when available. This study was conducted with appropriate institutional review board approval from both institutions.

Results

A total of 50 patients were included in the study, with one patient having two synchronous lesions. The clinicopathologic features in our patients are summarized in Table 1. Tumors ranged in size between 0.2 and 8.0 cm, with a mean size of 2.1 cm. Most patients

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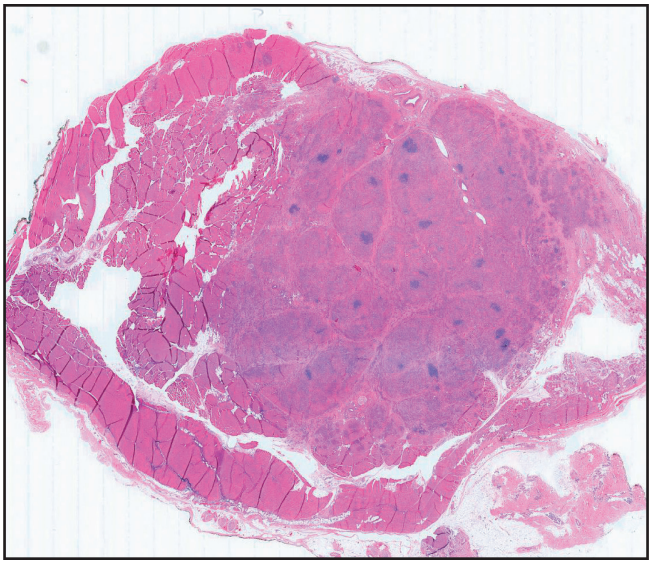

Image 1 Scanning magnification of granular cell tumor arising within skeletal muscle shows an expansile nodule (right half of field) that blends imperceptibly with the surrounding skeletal muscle (H&E, ×2).

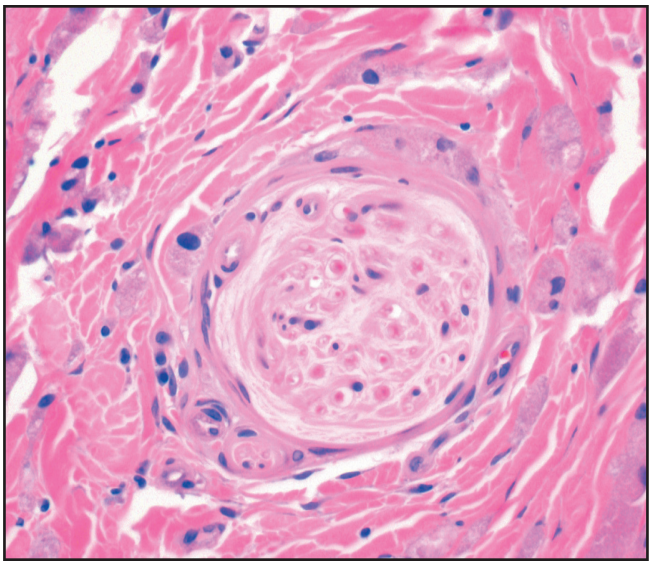

Image 2 Small entrapped nerve trunk within the tumor shows subtle perineurial infiltration by granular cells (H&E, ×40).

were women (64.0%). The mean age at the time of excision was 38.6 years, with a range from 5 to 69 years. The tumors were located in many different body sites, including the arms (15.7%), hands (15.7%), chest (15.7%), legs (11.8%), head (7.8%), axilla (7.8%), back (5.9%), flank (5.9%), feet (5.9%), vulva (3.9%), and buttock (3.9%). There was a clear predilection for the upper extremities and upper torso (31.4% and 19.6% of tumors, respectively). Most tumors were located in the subcutaneous tissue above the fascia, although seven (13.7%) were located entirely or primarily within muscle.

All cases showed the classic histologic features of GCT, including nests and sheets of large polygonal cells with abundant coarse granular eosinophilic cytoplasm. Nuclei were centrally located and ranged from small and dark to large with vesicular chromatin. Most cases showed an infiltrative growth pattern (58.8%), and positive margins were commonly seen (68.2%). The tumors arising in muscle had irregular borders that blended imperceptibly with the surrounding skeletal muscle fibers **Image 1**. Perineural involvement by tumor cells was appreciated in four cases **Image 2**. Three cases showed multinucleated giant cells with nuclei arranged at the periphery similar to Langhans giant cells. Eighteen (35.3%) cases showed tumor-infiltrating lymphocytes, indicating an immune response to the tumor **Image 3**. The lymphoid infiltrates were small and well circumscribed and devoid of lymphoid follicles with germinal centers. Tumors arising in the subcutaneous fat showed irregular, infiltrating borders **Image 4** and **Image 5**. Tumors with features that would qualify for a diagnosis of malignant GCTs were not seen, but 11 (21.6%) cases fulfilled the criteria for atypical GCTs, including enlargement of nuclei with prominent nucleoli, mitotic figures, and spindling of the tumor cells **Image 6** and **Image 7**. Six (11.8%) cases showed only focal atypia, although the atypia was not enough to qualify for an atypical GCT. All cases were tested by immunohistochemistry for S-100 protein, which was positive in all cases. Long-term follow-up was available in only 11 patients; two (18%) of 11 patients had local recurrences. One patient had a recurrence after 3 years. The other had a documented history of GCT 5 years prior to the local recurrence reviewed for this study. Information regarding second surgery for control of positive margins could be obtained in only four cases; none of those four patients with documented wider excisions developed recurrences.

Discussion

GCTs were first described in 1926 by Abrikossoff,[8] and since then, there have been numerous large case series characterizing this lesion.[1,4] In all these series, the tumors were mainly from the skin and mucosal sites. GCTs arising primarily in superficial and deep soft tissue are rare and have not been thoroughly studied. The largest case series

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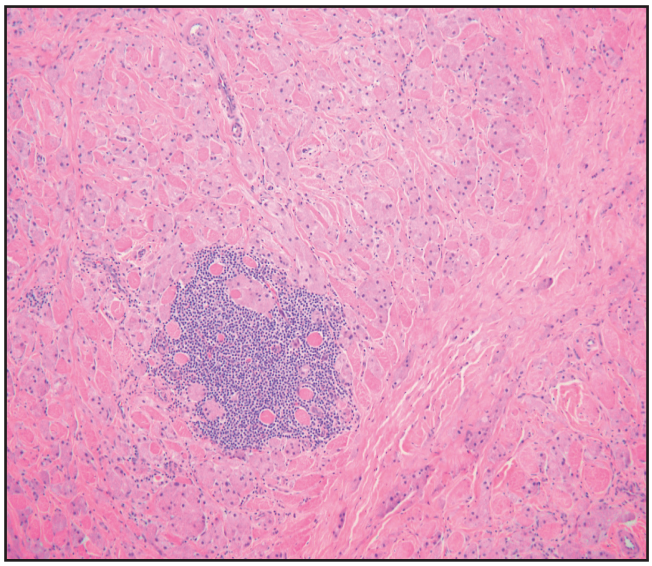

Image 3 This tumor shows a focal lymphoid aggregate composed of small lymphocytes. The lymphoid infiltrates may be an indication of an immune host response to the tumor (H&E, ×4).

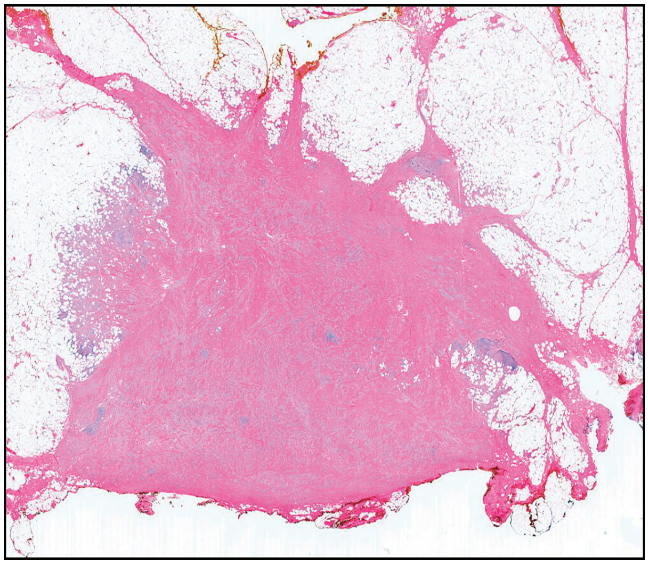

Image 4 Scanning magnification from a tumor that arose in the subcutaneous fat shows an irregular, stellate configuration with small islands of granular cells invading the fat (H&E, ×1).

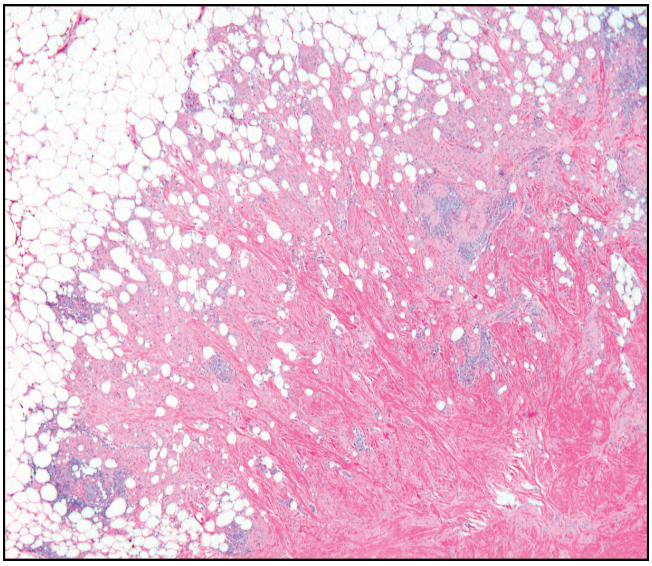

Image 5 Higher magnification from area infiltrating the fat shows irregular entrapment of adipocytes by the granular cells in the vicinity of the main tumor mass (H&E, ×10).

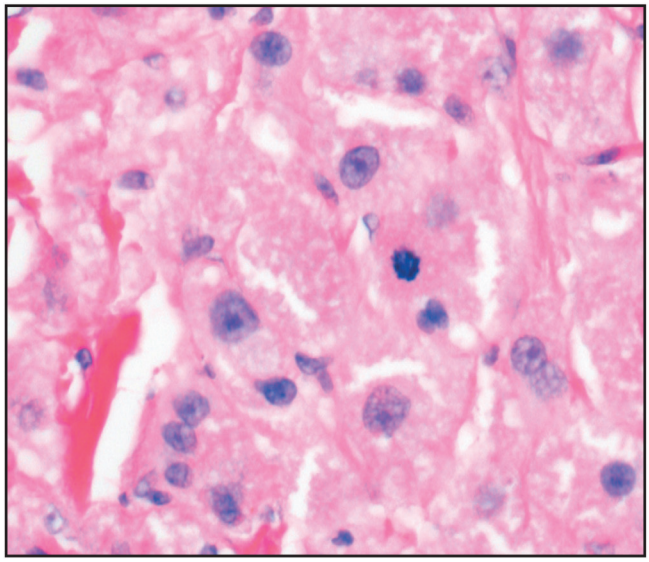

Image 6 Atypical granular cell tumor arising in muscle shows enlarged nuclei with prominent nucleoli and a mitotic figure (H&E, ×60).

of benign soft tissue GCTs found in the English-language literature was by Rose et al[5] in 2009, which described 11 cases in 10 patients. Our data add to this to further characterize soft tissue GCTs with 51 additional cases.

Soft tissue GCTs are generally comparable to GCT tumors overall. Patients' mean age at presentation has been reported between 32 and 38 years based on large studies.[1,4] A mean age of 38.6 years was noted in our study, which falls close to this range. GCT tumors typically show a female predominance, which ranges from 1.8 to 2.9:1,[1,3,7] and this predilection was maintained in our study (1.8:1).

There were a few noticeable differences present in the subset of soft tissue GCT in this study compared with those reported in the skin and mucosal surfaces. It is well established that GCT can be infiltrative and that positive margins are common. However, of the patients with evaluable resection margins in our series, 68.2% were positive, which is notably higher than previously reported for dermal tumors

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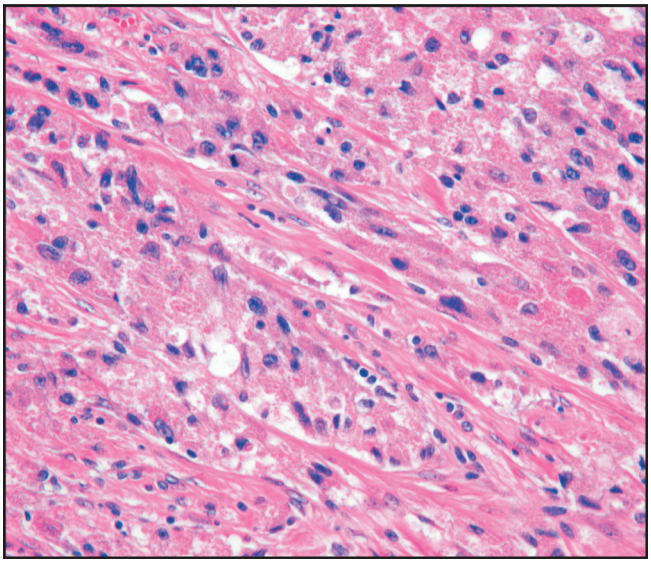

Image 7 Atypical granular cell tumor in subcutaneous location shows focal spindling of the tumor cells admixed with more conventional epithelioid tumor cells (H&E, ×40).

(43%).[1] This high number may be related to difficulty of procedure, due to anatomic locations or depth of the lesions, or perhaps a higher frequency of infiltrative growth pattern (58.8% of tumors in our study). The size of GCTs was larger than average: 2.1 cm in our study compared with 1.2 cm and 1.85 cm in other large series.[1,4] This propensity toward larger size in soft tissue tumors has been noted before with averages of 3.8 cm and 4.6 cm in two smaller cases series.[5,9] Larger tumor size has also been shown to correlate with a worse outcome.[10] Other studies[1,5,6] showed an incidence of multiple GCTs between 5% and 16%, which is higher than the 2% noted in our study, although this is not surprising as only soft tissue tumors were included in our study.

GCTs can rarely be malignant, which historically has accounted for about 2% of all GCTs.[6] Fanburg-Smith et al[10] defined the histologic criteria of malignancy by examining a subset of soft tissue GCTs that had features concerning for malignant behavior. Their study defines malignant GCT as having at least three of the following features: necrosis, spindling of tumor cells, vesicular nuclei with large nucleoli, increased mitotic rate (greater than two mitoses/10 high-power fields), high nuclear to cytoplasmic ratio, and pleomorphism. However, it has been noted that histologically benign-appearing tumors can metastasize.[11,12] In our study, there was a single case with three of the listed features, but due to the tumor's small size, superficial location, and noninfiltrative margins, it was felt that a malignant diagnosis was inappropriate and therefore it was called atypical. There were 10 other cases of atypical GCTs (21.6% total), which are defined as having only one or two of the above features. This is comparable to the study by Rose et al[5] of 11 cases of soft tissue GCTs, which found two (18%) that fit the criteria for atypia. In addition, six (11.7%) other cases showed focal atypical features, although not enough to fulfill the criteria set by Fanburg-Smith et al.[10] It is unknown how often GCTs have only focal atypia, as this has not been addressed in the literature.

Most of our cases occurred in the subcutaneous soft tissue (86.3%), with only seven (13.7%) found in intramuscular locations. This contrasts with Rose et al,[5] who found five (45.4%) of 11 cases in their study within muscle, and the study by Elkousy et al,[13] who reported two (20%) of 10 cases of soft tissue GCT as being located within the thigh muscles. This discrepancy may be due to sample size. The report by Rose et al[5] noted that three (27%) of 11 atypical cases occurred in the upper extremity, which is similar to that noted in our study (31.4%). This finding is unexpected given the mass and surface area of the upper extremities compared with the rest of the body, and its biologic rationale and significance are unclear. Two (18%) of 11 patients with adequate follow-up in our study had recurrences, which is higher than previously reported for GCTs overall (8.9%).[1] One of the recurrences corresponded to a patient with a large (2.5 cm) lesion with positive margins; the tumor was of conventional type and devoid of cytologic atypia. The second case of recurrence corresponded to one of the cases included in this study for which the original initial resection specimen was not available for review; the histology of the recurrent tumor was also of conventional type without cytologic atypia. The incidence of recurrence in our study may be overrepresented given that most patients were unavailable for follow-up. Given that none of the "atypical" cases in our series recurred, it is possible that the presence of atypical features may not be clinically significant in this type of tumor. Further studies with long-term follow-up in atypical tumors may be indicated to confirm this impression.

We have presented the largest case series to date describing benign and atypical soft tissue GCTs. Overall, GCTs of soft tissue showed some notable differences from their dermal and mucosal counterparts. They tend to be larger, more infiltrative, and more often have positive margins. GCTs of soft tissue are often atypical, and many cases of malignant soft tissue GCTs have been identified in the literature. In addition, a higher recurrence rate than dermal GCTs was noted in the patients available for follow-up. These findings suggest that GCTs of soft

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tissue should be followed closely as they may behave more aggressively.

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