The Growth Factors of Subcutaneous Benign Lipoma: Consideration from Anatomical Position of Occurrence

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Background: Subcutaneous lipomas are the most common benign soft-tissue tumors. Theoretically, adipocyte sites could be the primary foci; however, lipomas are likely located in the occipital, neck, shoulder, torso, and thigh areas. To date, no study has reported the anatomical relationship between these subcutaneous structures and lipomas. Therefore, we aimed to investigate the anatomical locations of lipomas and considered their growth factors. In addition, we discussed the mechanism of fat amplification to improve the success of fat grafting.

Methods: In the present study, lipomas measuring more than 5 cm in diameter from patients hospitalized between 2017 and 2021 were retrospectively examined using preoperative computed tomography and magnetic resonance imaging as well as clinical records with intraoperative pictures.

Results: In total, 22 lipomas of 22 patients were examined. All lesions (100%) were accompanied by neurovascular perforators. Nineteen lesions (86%) were located deep in the superficial fascia, where it was clearly defined. Moreover, all lesions were located at the mobile adipofascial layer adjacent to an anchored fixed or less mobile structure.

Conclusions: Lipoma growth might require neurovascular perforators that supply both blood flow and continuous stretching stimuli. The mobile adipofascial layer with bones adjacent to a fixed or less mobile area might also be necessary to grow lipomas. If these findings can be used as clues to elucidate the mechanism of fat amplification in the future, it may lead to an improvement in the survival rate of fat grafts. *(Plast Reconstr Surg Glob Open 2022;10:e4524; doi: 10.1097/GOX.0000000000004524; Published online 23 September 2022.)*

INTRODUCTION

Subcutaneous lipomas are the most common benign soft-tissue tumors, with a historical predilection in middle-aged women.[1] This is known as an ipsilateral, discrete, or benign tumor in many cases. Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) revealed homogenous adipose density. Lipomas are of mesenchymal origin and expand not invasively but exclusively against adjacent organs. Theoretically, lipomas can originate anywhere in the body along with the distribution of adipocytes, but subcutaneous lipomas are commonly situated in certain areas (eg, occipital, neck, shoulder, torso, and thigh), suggesting a certain site-specificity.[1]

The primary foci of lipomas among the extensively distributed subcutaneous fat layer remain unknown; however, Minabe et al[2] reported that lipomas of the frontal forehead originated adjacent to the supraorbital or supratrochlear neurovascular bundle deep into the frontal muscle, which is homologous to the superficial fascia in embryology. Likewise, lipomas in another area could clinically sit along the cutaneous neurovascular perforators and superficial fascia. However, to our knowledge, no work to date has described the anatomical relationship between these subcutaneous structures and lipomas.

Therefore, this study aimed to investigate the relationship between lipoma development and specific tissues, such as the blood vessels, nerves, and fascia by retrospectively examining preoperative CT and MRI findings as well as operative records with intraoperative pictures. Hence, the anatomical characteristics and growth factors can be considered by creating a map.

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

MATERIALS AND METHODS

Clinical Findings and Image Analysis

Subcutaneous benign lipomas were diagnosed based on the clinical course, physical examinations, and preoperative CT and MRI findings. Benign lipomas are generally asymptomatic and grow gradually. They are physically elastic, soft, and mobile subcutaneous masses. To rule out malignancy, such as liposarcoma, CT (noncontrast or contrast) and MRI (noncontrast) were performed if the lipoma was more than 5 cm in diameter.[2–4]

We defined perforators along which lipomas were situated based on noncontrast MRI as follows: 1–2-mm linear structures with a consistent diameter throughout its course, low-signal intensity in high-signal lipoma on T1-weighted (T1W) images, high-signal intensity in isosignal lipoma on T2-weighted short-tau inversion recovery (T2 STIR) images, and traceable to the subfascial vessels retrogradely (Fig. 1A, B).[5]

Superficial fascia appeared on MRI findings as low-signal-intensity lines parallel to the skin on T1W and T2 STIR images, thereby confirming a relationship between superficial fascia and lipoma. CT images of the superficial fascia similarly revealed a high-density thin membranous structure separating two layers of subcutaneous fat (Fig. 1A, C).

Patient Characteristics

Twenty-two cases of ipsilateral discrete subcutaneous benign lipomas were identified. We limited the examined cases to lipomas measuring more than 5 cm, for which CT and MRI data were preserved. They were operated on at the Department of Plastic Surgery at Saitama Medical Center between January 2017 and August 2021 and analyzed retrospectively. In particular, lipomas that appeared in the craniocervical part or torso of the body were chosen because these parts are mostly distinct from the two-layered structure of the adipose tissue according to Nakajima et al.[6]

Ethical Approval of Studies/Informed Consent

This study was approved by the institutional review board of Saitama Medical Center (No. SOU2021-123).

Takeaways

Question: The primary foci of subcutaneous lipomas among the extensively distributed subcutaneous fat layers are still unknown. No study has reported the anatomical relationship between different subcutaneous structures and lipomas. This study aimed to reveal the anatomical locations of lipomas and discuss their growth mechanisms.

Findings: Twenty-two lipomas were retrospectively examined using preoperative computed tomography and magnetic resonance imaging and intraoperative pictures. Lipoma growth might require neurovascular perforators. The mobile adipofascial layer with bones adjacent to a fixed or less mobile area might also be necessary for lipoma growth.

Meaning: Neurovascular perforators and the superficial fascia are anatomically important for lipoma growth.

It was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Surgical Procedure

Under general or local anesthesia, the lesion was excised through either an adequate skin incision for open resection or semiclosed resection assisted with a surgical aspirator and endosocope.[2,7] If the lipoma was located in an exposed area and the patient was keen for a better cosmetic outcome, semiclosed resection using an ultrasonic surgical aspirator (SONOPET, Stryker, Kalamazoo, Mich.) with or without an endoscope was considered. This ultrasonic device can resect the adipose tissue while preserving the nerves and blood vessels.[2,8]

Statistical Analysis

All statistical analyses were performed using the EZR system (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for
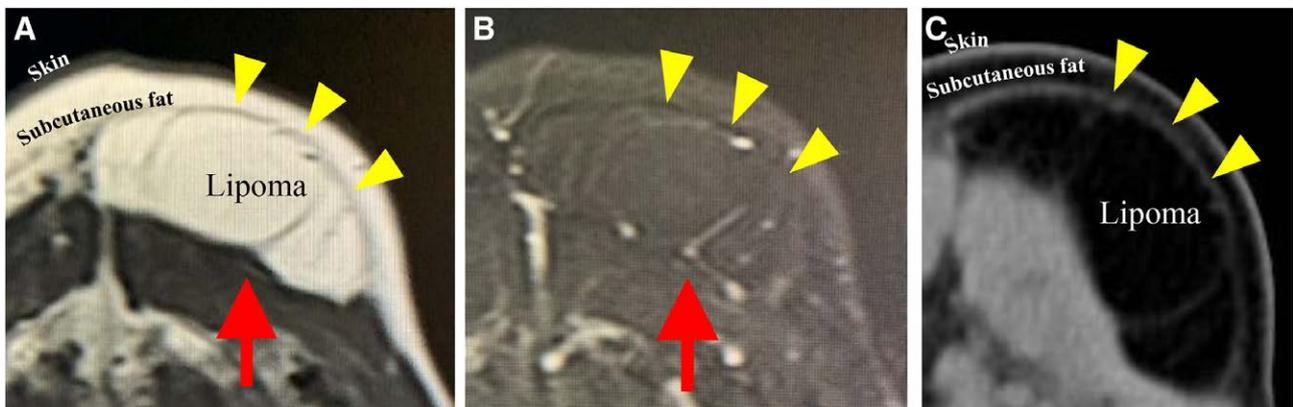

Fig. 1. MRI/CT image analysis. A, Axial T1W image. B, Axial T2 STIR image. C, Axial noncontrast CT image of posterolateral neck lipoma. A 1–2-mm linear structure with no irregular diameter, an obvious low-signal area in T1W, and a high-signal area in T2 STIR was identified as a vascular perforator (red arrows). It could be traced continuously to the subfascial source vessel. The lipoma is located in the subcutaneous fat layer deep into the superficial fascia (yellow arrow heads).

Table 1. Patient Characteristics

Case	Age (y)	Sex	Size (cm)	Site of Craniocervical Part and Torso	Corresponding Nerve and Vessels	Operative Method
1	49	F	5.1×2.2	Mental (Rt)	Mental	Open resection
2	63	F	7.5×6.0	Scapula (Rt)	Fourth intercostal	Ultrasonic aspirator
3	44	F	7.2×3.5	Scapula (Rt)	Fourth intercostal	Ultrasonic aspirator
4	73	F	8.2×4.9	Occipital (Lt)	Occipital	Open resection
5	63	M	6.4×3.9	Occipital (Rt)	Occipital	Ultrasonic aspirator
6	40	F	5.1×5.0	Mental (Rt)	Mental	Open resection
7	60	F	5.5×3.4	Axilla (Rt)	Third intercostal	Open resection
8	49	M	7.1×3.1	Clavicular (Rt)	Supraclavicular	Open resection
9	51	F	7.5×5.0	Lumber (Lt)	Tenth intercostal	Open resection
10	43	F	5.2×2.7	Clavicular (Lt)	Supraclavicular	Ultrasonic aspirator
11	31	F	11.7×5.6	Scapula (Rt)	Fifth intercostal	Ultrasonic aspirator
12	54	F	7.0×3.0	Scapula (Lt)	Sixth intercostal	Ultrasonic aspirator
13	66	M	6.0×4.5	Occipital (Lt)	Occipital	Open resection
14	77	F	9.0×7.0	Occipital (Rt)	Occipital	Open resection
15	45	M	9.6×3.6	Scapula (Lt)	Fourth intercostal	Ultrasonic aspirator
16	54	F	7.0×7.0	Axilla (Rt)	Third intercostal	Ultrasonic aspirator
17	54	F	6.8×3.1	Clavicular (Rt)	Supraclavicular	Ultrasonic aspirator
18	56	F	7.9×2.7	Lumber (Rt)	Ninth intercostal	Open resection
19	24	F	5.2×3.5	Scapula (Lt)	Fourth intercostal	Ultrasonic aspirator
20	48	F	7.3×3.9	Axilla (Rt)	Fourth intercostal	Ultrasonic aspirator
21	36	F	5.5×2.3	Scapula (Lt)	Fifth intercostal	Open resection
22	60	M	9.9×4.5	Axilla (Lt)	Third intercostal	Ultrasonic aspirator

F: female; M: male.

R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.[9] Statistical analysis was performed to determine whether there was a significant difference in the lipoma region according to age, sex, and size. The t test was performed for ordinal scale variables (age and size), and Fisher exact test was used for sex (nominal variable). The level of significance was set at P less than 0.05.

RESULTS

The study included 17 women and five men. The mean age of the patients was 52 (range, 24–77) years. The characteristics of the 22 patients are presented in Table 1. Regarding the craniocervical lipomas, there were six cases (27%), which were composed of four occipital and two mental cases, and as for the torso, there were 16 cases (73%), composed of seven scapular, four axillary, three clavicular, and two lumbar cases. A 31-year-old woman with a scapular lipoma over 10 cm had a history of enlargement during pregnancy (case 11). All these areas were subjected to mechanical stretching stimulation by joint movement. The surgical procedures used in the 22 patients were as follows: 12 (55%) and 10 patients (45%) underwent ultrasonic aspiration and open resection, respectively.

According to the surgical records and pictures, vascular perforators penetrated the lipoma in nine lesions (41%). Among these nine lesions, three (33%) had accompanying cutaneous nerves along with the vessels, and intraoperative images were captured in the endoscopic view (Fig. 2A; Table 2). It is possible that cutaneous nerves might have accompanied other cases but were not noted in the surgical records or were too thin to be cut during resection. Subcutaneous fibrous septa were partially shown as a connective tissue framework that protected the neurovascular

Table 2. Anatomical Relationship of Lipomas with the Cutaneous Perforators and Superficial Fascia

Total (22 Cases)	Surgical Records	CT	MRI
Cutaneous vascular perforator (%)			
Identified	9/22 (41)	15/22 (68)	22/22 (100)
(Along with a cutaneous nerve)	3/9 (33)	N/A	N/A
Not identified	13/22 (59)	7/22 (32)	0/22 (0)
Superficial fascia			
Undefined	N/A	3/22 (14)	
Deeper lipomas	12/12 (100)	19/22 (86)	

N/A, not applicable

perforators. They were preserved in the cases using an ultrasonic aspirator. The thicker venous perforator with a venous valve and thinner arterial perforator, both containing blood inside, were noticed together with the white nerve perforator.

Intraoperative pictures also revealed that the lipomas were often exposed after incising the superficial fascia (Fig. 2B). The anatomical relationship with the superficial fascia was described in 12 out of 22 lipomas (55%), all of which were located deep in the superficial fascia (Table 2). It was also documented that the superficial fascia was sutured with three-layer wound closure.

In this study, the preoperative CT/MRI images of 22 cases were retrospectively analyzed to determine whether the cutaneous neurovascular perforators and the superficial fascia were noticeably depicted. All MRI (100%) and 15 CT scans (68%) revealed cutaneous perforators running through the lipoma. Nineteen lesions (86%) were deep into the superficial fascia, and three lesions (14%) had no anatomical relationship with the superficial fascia on CT/MRI (Table 2).

To summarize our results, we mapped the anatomical positions of 22 lipomas and considered neurovascular perforators; our map was based on arterial perforators in "the angiosome concept" proposed by Taylor and Palmer[10]
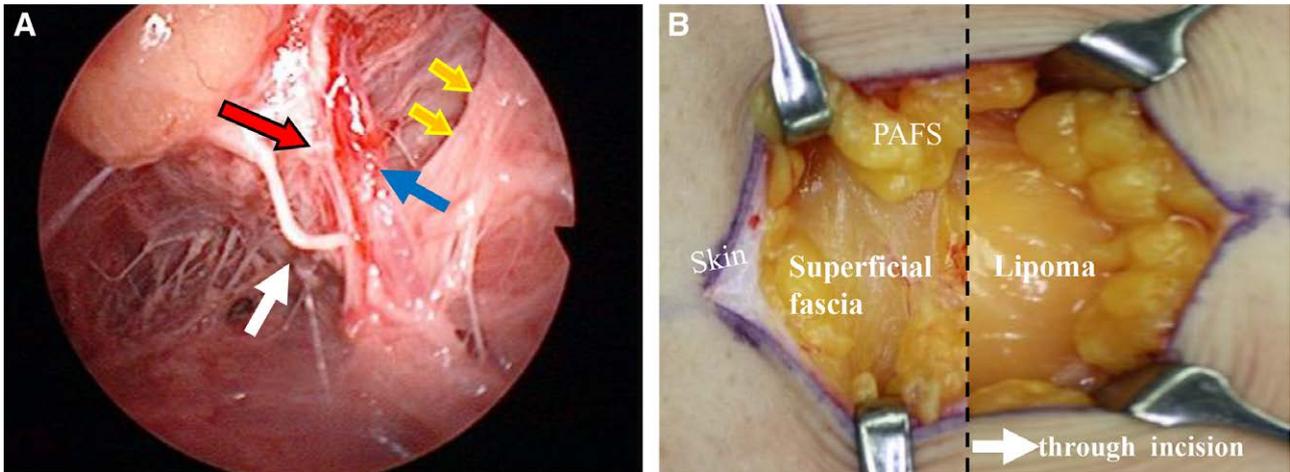
Fig. 2. Intraoperative view in the surgical records. A, Endoscopic image after lipoma resection assisted with surgical aspirator of a scapular lipoma. The preserved artery (red arrow), vein (blue arrow), and nerve (white arrow) demonstrate the fifth intercostal neurovascular perforator. Some septa of the connective tissue were also preserved (orange arrows). B, Subcutaneous fat appeared just above the superficial fascia (left). Lipoma was exposed through incising the superficial fascia (right). * Adipose tissue above the superficial fascia.

and Taylor and Minabe.[11] Their perforator maps revealed a detailed plot of the arterial perforators of 0.5 mm or greater throughout the body with superficial muscles outlined to indicate the exact perforating position. The subcutaneous vessels and nerves anatomically often accompany each other in the head, neck, and torso.[12] Therefore, in our maps, we plotted the sites of the 22 lipomas and annotated them according to the color-coded neural areas (Fig. 3).[13] In all 22 cases, lipomas were generated at the same site as the neurovascular perforators, such as mental
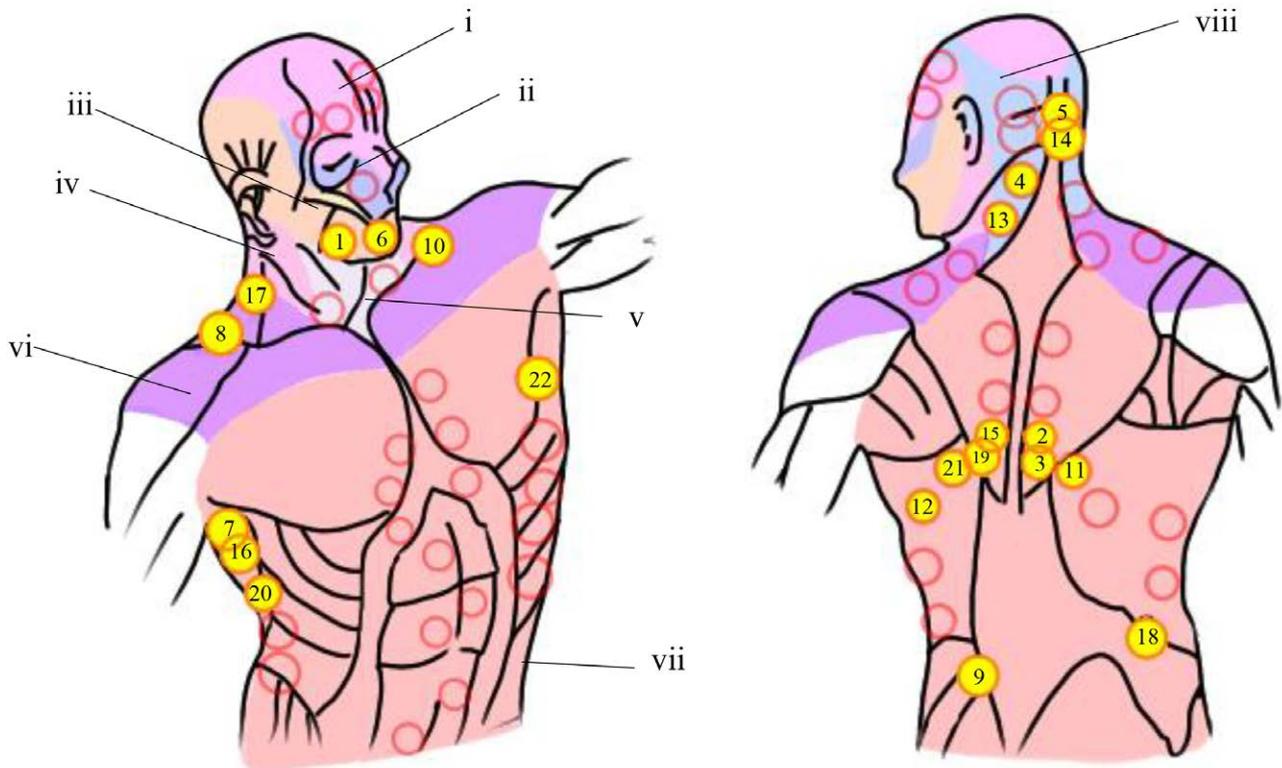

Fig. 3. Lipoma maps on neurovascular perforators. A, Anterior view of the body. B, Posterior view of the body. Red open circle: neurovascular perforators based on "angiosome maps";[10] yellow closed circle: lipomas on the perforator maps with numbers corresponding to the case numbers in Table 1. All lipomas matched the site of the neurovascular perforators. The skin was color coded according to each sensory neural area. i: ophthalmic; ii: maxillary; iii: mental; iv: great auricular; v: transverse cervical; vi: supraclavicular; vii: intercostal; viii: occipital. (The figure with muscular outlines arranged after Reference 10.)
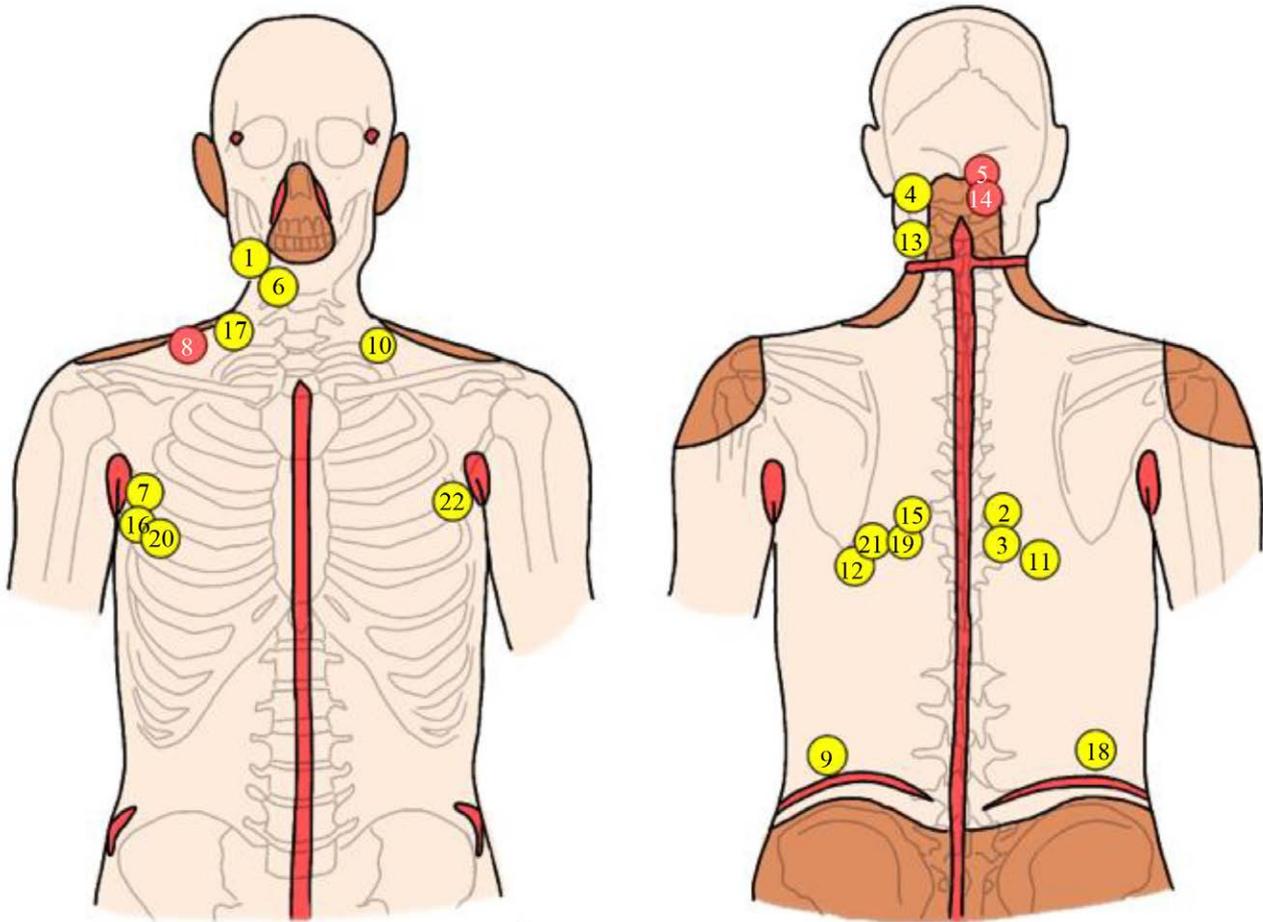
Fig. 4. Lipoma maps relevant to the subcutaneous adipofascial structure. A, Anterior view of the body. B, Posterior view of the body. Red circle: lipomas in the indiscernible adipose layer and yellow circle: lipomas deep into the superficial fascia with numbers corresponding to the case numbers in Table 1 and Fig. 3. The skin is color coded according to the structure of the adipofascial tissue[6]; beige: two-layer mobile structure with clear superficial fascia; brown: one layer less mobile structure with unclear superficial fascia; red: anchoring fixed structure with no superficial fascia (the figure with bony outlines arranged after Reference 6).

perforators, occipital perforators, and dorsal or lateral intercostal perforators. There was no lipoma on the anterior intercostal perforators or on the epigastric perforators in the medial-anterior torso region of the map.

In contrast, on other maps, we plotted the lipomas, thus revealing the anatomical structure of the subcutaneous adipofascial tissue, whether mobile with clear superficial fascia or less mobile or fixed without clear superficial fascia. Three degrees of tissue mobility were color coded according to the classification reported by Nakajima et al[6] (Fig. 4). The maps also show anterior or posterior bony outlines of the head, neck, and torso, indicating tissue mobility around the joints. Nineteen lesions (86%) deep into the superficial fascia were in the areas of two adipose layers, such as the torso, except for the anterior or posterior midline (yellow circles in Fig. 4). Conversely, three lesions (14%) appeared with no anatomical relation with the superficial fascia in the area with indiscernible adipose layers, such as the posterior neck and deltoid area (red circles in Fig. 4). The mapped lipomas tended to grow in areas with a mobile adipofascial layer adjacent to the anchored fix or a less mobile structure.

The relationship between the site of the regions and each factor was statistically analyzed (Table 3). The regions were categorized into two groups: the craniocervical region and the torso.

Age

The mean ages of patients with a lipoma in the craniocervical region and the torso were 61.3 (range, 40–77) and 48.3 (range, 24–63) years, respectively. Older patients tended to have lipomas in the craniocervical region ($P = 0.0308$).

Sex

Among the 22 patients, 17 women (77%) and five men (23%) were included. There was no statistical correlation between sex and region ($P = 0.585$), which might have been consistent with the description of sex in the lipoma report by Adair et al.[1]

Table 3. Statistical Analysis of the Association between the Region and Each Factor

	Overall	Craniocervical Part	Trunk	P
1. Age (y)	51.8±12.9	61.3±14.2	48.3±10.8	0.0308*
2. Sex (male/female)	5/17	2/4	3/13	0.585
3. Size (cm)	7.4±1.7	6.6±1.6	7.4±1.8	0.389
4. Region (%)	100	Occipital 18	Scapula 32	N/A
		Mental 9	Axilla 18	
			Clavicular 14	
			Lumber 9	

*Statistical significance
N/A, not applicable.

Size

The mean tumor size in the craniocervical region was 6.6 cm (range, 5.1–9.0 cm in the longer axis), while that of the torso was 7.4 (range, 5.2–11.7) cm. There was no statistical correlation between size and region (P = 0.389).

DISCUSSION

Benign adipocytic neoplasms broadly encompass subcutaneous lipoma, intramuscular lipoma, lipomatosis, lipomatosis of the nerve, lipoblastoma, and angiolipoma. Among these categories, subcutaneous lipoma is the most common.[14] Because of its histopathological benign and asymptomatic characteristics, its primary foci have remained unclear.

In this study, it was elucidated that the subcutaneous lipoma was accompanied by a neurovascular perforator, as shown in Fig. 3.

Regarding the relationship between blood vessels and lipoma, only one case report described an intramuscular lipoma around a vascular perforator in the vastus lateralis muscle during anterolateral thigh flap elevation.[15] Adipose tissues cannot grow without blood flow; therefore, fat grafting can survive well around blood vessels.[16]

Findings regarding the relationship between nerves and fat have also been reported.[17] Sensory nerve expression in perivascular adipose tissue has been confirmed via animal experiments.[18] Nerve-derived mesenchymal stem cells might suggest a role for nerves in the development of lipoma.[19]

Lipomas tend to grow in areas that receive continuous stretching, but the exact mechanism remains unknown.[20,21] All of the lipomas in this study were observed in regions, such as the mouth, neck, shoulder/axilla, scapular, or lumbar, which received continuous stretching stimuli. Therefore, these results support the hypothesis that lipomas might grow in the area where the movement of the bones, such as the mandible, cervical spine, clavicle, rib, scapula, and ilium, is similar to that of the joints, and could also provide the moving stimuli to the subcutaneous adipofascial tissue. In contrast, there was no lipoma in the anterior chest and abdomen because the sternum could not act as the joint, and there was no bone in the abdomen, although the anchoring adipofascial structure was defined in the centerlines of the torso (Fig. 4). Especially, the mobile area with bones adjacent to the fixed points raised lipomas gradually, which demonstrated that lipomas did not arise on the neurovascular perforators aligned in the anterior midline (Fig. 3).

According to Sunderland,[22] in areas prone to mechanical stimulation, the perineural fat grows as a cushion to protect the nerves. It is possible that continuous stimuli activate mechanoreceptors that are already known as peripheral nerve endings, such as Meissner's corpuscle, Pacini corpuscle, Merkel's disc, and Ruffini corpuscle,[23] and their neural activation might become the signal for the fat cells to grow. However, MacGregor and Dyson[24] suggested that if a continuous stimulus is a trigger for fat growth, lipomas would then occur in a larger area. Our findings suggest that lipoma growth is dependent on stretching stimuli, vascular flow, and the structure of the surrounding adipose tissue.

Lipomas were situated adjacent to the superficial fascia in all cases, and 86% of them were deep into the superficial fascia (Fig. 2B). According to Nakajima et al,[6] subcutaneous fats could be divided into two major layers bordered by the superficial fascia: the "protective adipofascial system" (PAFS) above and the "lubricant adipofascial system" (LAFS) below. The fat cells in the PAFS are tightly connected to the skin and have very limited mobility, whereas mobility in the LAFS is achieved by loose fibrous capsules.[6,25,26] One of the reasons why subcutaneous lipomas are more likely to occur in the LAFS could be that its loose and lubricating properties allow lipomas to expand.[1] In this study, 86% of lipomas were in the LAFS. Sometimes, lipomas exposed immediately below the skin could be experienced in regions, such as the deltoid and posterior neck. These areas have no obvious superficial fascia dividing the subcutaneous adipofascial tissue, and the part of the PAFS tends to receive stretching stimuli from the surrounding joint movements.

Fat accumulation in obesity, often caused by overnutrition, can occur anywhere in the adipocytes. Adipose tissue increases the centrality and systemic involvement of the whole body.[27] In contrast, subcutaneous benign lipomas occur as discrete and ipsilateral tumors and have little relation to nutrition.

Multiple symmetrical lipomatosis is thought to be associated with abnormal lipid metabolism due to heavy alcohol consumption.[28] The adipose tissue is symmetrically localized on the anterior neck and bilateral shoulder/trunk, presenting the typical appearance of a "horse collar" or "buffalo hump." The fat tissue could often accumulate in the superficial subcutaneous layer,[29] that is diffuse, nonencapsulated adipose tissue proliferation in the subcutaneous bed, the boundary of which remains unclear.[30] Because of the multiple and symmetric nature, this lipomatosis differs from the subcutaneous lipomas investigated in this study.

Considering the amplification of fat, the relationship with female hormones should be discussed. Most of the lipomas in this study occurred in women, as reported by Adair et al.[1] One of the female hormones, estrogen, plays a role in amplifying subcutaneous fat and promoting visceral fat metabolism.[31,32] Among the 22 cases, there was a case of lipoma enlargement due to pregnancy (case 11 in Table 1). Therefore, female hormones might play a role in the growth of lipomas and subcutaneous fat.

In this study, the growth factors of lipomas have been discussed based on the anatomical location of lipoma. The theory of fat amplification in lipomas may apply to fat grafting. Various methods of fat grafting are currently being developed to increase the survival rate in combination with biology, such as mixing adipose-derived stem cells.[33] However, it is still expensive to be applied clinically. We hypothesized that lipomas grow in a deep mobile adipofascial layer near the neurovascular perforator. Therefore, if fat grafting with fat injection is performed near the neurovascular perforator in the deep mobile adipofascial layer, the grafting rate may improve. This needs verification in future studies.

This study had some limitations. First, it focused on the anatomical relationship between lipoma and blood vessels, nerves, and superficial fascia. Therefore, this must be clarified in future studies, as our study did not directly indicate the exact origin of lipomas. Second, we only hypothesized the growth of lipoma based on the relationship between lipoma and the surrounding structures, and we did not elucidate the mechanism of fat amplification. Elucidation of this mechanism in the future may help increase the survival rate of fat grafts.

CONCLUSIONS

Subcutaneous lipomas might grow around the neurovascular perforators, which include the sensory nerves that could receive mechanical stretching stimuli and blood vessels that could provide sufficient blood flow. Lipoma growth might also require loose adipose tissue and mobile bone adjacent to the fixed area. We believe that if the mechanism of fat amplification is elucidated in future studies, it may provide a basis for establishing the etiology or clinical treatments, thereby contributing to improving fat grafting methods.

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