Benign Skin Lesions: Lipomas, Epidermal Inclusion Cysts, Muscle and Nerve Biopsies

Kartik A. Pandya, MD,*, Frederick Radke, MD, FACS

LIPOMAS AND EPIDERMAL INCLUSION CYSTS

Overview

Common surgical procedures done in the minor operating room or in the office include removal of lumps, bumps, and biopsies. Removal of superficial masses and epidermal cysts is frequently performed at the request of patients for cosmetic purposes, but is occasionally done due to diagnostic insecurity. These lesions include benign and malignant varieties as well as solid and cystic lesions.

Lipomas are benign skin tumors composed of mature fat cells and are the most common subcutaneous tumors.1 Although many of these can be removed in the surgical clinic or minor operating room, some require more advanced preoperative planning and more complicated resection. The diagnosis, pathology, and treatment of benign tumors, and other commonly associated tumors that may require a more substantial workup and operative intervention, are discussed.

Epidermal inclusion cysts are benign skin lesions that arise from obstructed or ruptured pilosebaceous follicles that can also be excised locally.2 In some cases an associated infection or foreign body reaction can occur if the cyst contents are spilled into the surrounding tissues, and therefore their treatment is slightly different from that of simple lipomas.3 Epidermal inclusion cysts are also known as sebaceous, epithelial, keratin, and epidermoid cysts.2 The term sebaceous cyst is commonly used but is inaccurate due to the absence of sebum within the cyst. The term used here is epidermal inclusion cyst.

* Corresponding author.
E-mail address: pandyk@mmc.org (K.A. Pandya).

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Other minor procedures such as nerve and muscle biopsies may be performed to diagnose neuromuscular diseases.

**Diagnosis**

Lipomatous masses include simple lipomas, angiolipomas, well-differentiated lipomas, and liposarcomas. Another variant, the “atypical lipoma,” is also noted in the literature, with histologic similarities to the well-differentiated liposarcoma and propensity for local recurrence.

Complicated lipomas include masses found on imaging to have multiple septae or involvement of deeper structures and nerve involvement. These are normally found to be well-differentiated lipomas, deep atypical lipomas, or liposarcomas.

Lipomas typically occur in the 40- to 60-year-old age group, but they can also occur in young children. Lipomas usually present as slow-growing masses without symptoms of pain or functional impairment. The incidence of lipomas is cited to be 2.1 per 1000 individuals. Lipomas are multiple approximately 5% of the time.

Patients presenting with a subcutaneous lipoma typically do not receive preoperative imaging. In cases of large lipomas (>5 cm), those irregular in shape, and those with symptoms of myofascial involvement, imaging is warranted using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Imaging should also be obtained if the tissue biopsy indicates the presence of an infiltrating mass.

MRI is the most sensitive imaging modality for lipomatous masses and has a high negative predictive value. On MRI, the fatty nature of the lipoma elicits a strong T1 signal; however, a large lipoma could be difficult to differentiate from a well-differentiated liposarcoma. MRI can be useful in the diagnosis of benign lipomas. Studies show a high positive predictive value for benign simple lipomas. The main criteria for determining a simple lipoma from more complicated masses are the presence of enhancing septae, nonadipose areas, and high T2 signal within the lesion. Gaskin and Helms report the difficulties associated with predicting well-differentiated liposarcoma from benign lesions, with the tendency to “over call” the lesion as a more aggressive entity.

Indications for removal of a lipoma typically include cosmetic concerns, but these tumors can also cause nerve impingement, pain, and consequent functional limitations that necessitate removal (such as with angiolipomas). Other indications for removal of lipomas include increase in size, irregular characteristics (induration), size (>5 cm), samples of core needle biopsy consistent with atypical features, or other features more consistent with a sarcoma (invasion/involvement of deep fascia).

Differential diagnosis of lipomas includes epidermal inclusion cyst, hematoma, vasculitis, panniculitis, rheumatic nodules, metastatic cancer/subcutaneous tumor, or infections.

Epidermal inclusion cysts also present as benign slow-growing masses but can also rupture before the patient seeks treatment. If the keratin-filled cyst ruptures, an intense foreign body giant cell reaction can occur, leading to pain and further swelling. Epidermal inclusion cysts have been associated with Gardner syndrome and individuals with extensive cysts should prompt a gastrointestinal neoplasm workup.

**Classification**

A simple lipoma may be watched clinically or removed in accordance with patient preference. The more invasive and histologic atypical lesions such as “atypical” lipoma, well-differentiated lipomas, and liposarcomas should be removed due to mass effects and, in the case of the liposarcoma, due to the propensity for systemic disease.
There are multiple classification schemes for lipomas depending on the anatomic location (face/back versus trunk/extremities). Lipomas can be classified in different morphologic categories, such as lipoma, angiolipoma, well-differentiated lipoma, and liposarcoma. Closely related tumors composed of immature fat cells and mature brown fat cells include lipoblastomas and hibernomas, respectively. Others classify lipomas as simple lipomas, fibrolipomas, angiolipomas, spindle cell lipomas, myxolipomas, and pleomorphic lipomas. Lipoblastomas are either circumscribed or diffuse and composed of immature adipocytes. They typically occur in the infant population and can histologically resemble a form of liposarcomas. Hibernomas are circumscribed tumors composed of mature brown fat tumors and histologically resemble fatty tumors in hibernating animals. Lipomas can also be broken down into simple lipomas and pleomorphic lipomas. Pleomorphic lipomas are more common on the neck and might require tissue sampling to arrive at the proper diagnosis. It is important to distinguish whether the lipoma is singular or one of multiple lesions, and to discern the presence of an associated syndrome. The subsequent histopathology will determine further follow-up with a more advanced surgical excision or referral to surgical oncology.

Syndromes associated with lipomas include adiposis dolorosa, benign symmetric lipomatosis (Madelung syndrome), Bannayan-Riley-Ruvalcaba syndrome, and Gardner syndrome, among others. Adiposis dolorosa is a genetic condition whereby patients present with multiple painful lipomas, and has a higher prevalence in women. This is sometimes misdiagnosed as simply a sporadic occurrence of multiple lipomas or neurofibromatosis. Benign symmetric lipomatosis, also known as Madelung disease, is a rare disorder affecting mostly men of Mediterranean descent. Patients develop significantly enlarged lipomatous masses that can be debilitating. Treatment consists of staged surgical resection and liposuction.

Cowden syndrome includes hamartomas affecting all three germ lines. These tumors can affect the endocrine (thyroid), skin (breast), and reproductive systems (endometrium).

Gardner syndrome is described as thyroid nodules, multiple epidermal inclusion cysts, osteomas, and intestinal polyposis. Recently it has been shown that the presence of intestinal polyps is required for an accurate diagnosis.

In cases of childhood lipomas, attention must be paid to the rest of the physical examination due to the higher incidence of associated developmental abnormalities. The syndromal states associated with lipomas in children include Bannayan-Riley-Ruvalcaba syndrome (BRRS) or Cowden syndrome, which are both associated with PTEN gene mutations. A child with associated classic BRRS findings of macrocephaly, hemangiomas, and speckled penis should warrant a more thorough genetic workup.

The epidermal inclusion cyst classification also includes other related entities such as trichilemmal cysts, milia, and steatocystoma multiplex. Although all result from obstruction of the pilosebaceous follicle, there are important histologic differences.

**Histopathology**

Fatty tumors are classified histologically according to their composition. The most immature fatty cell tumors are known as lipoblastomas, whereas tumors composed of brown fat are called hibernomas. A mature white fat tumor is known as a lipoma. Simple lipomas have a thick, well-defined capsule that is distinctly separate from the surrounding tissue. The location of lipomas can be varied, as they can be subcutaneous or invade the myofascial layers and be intimately associated with muscle and...
soft tissue. Further histologic subclassification of the lipoma depends on the tissue depth and involvement of other structures.

Spindle cell lipomas and pleomorphic lipomas are associated with dorsal, head, and neck distribution and histologically have collagen-forming spindle cells interspersed with adipocytes. Angiolipomas are composed of adipocytes with a vascular infiltration and are more commonly associated with pain and multiplicity, compared with other types of lipomas.12

Lipomas of the extremities are classified according to their involvement of subcutaneous and deep dermal tissues. For example, a lipoma involving the tendon sheath is classified as a synovium-related lipoma with tendon sheath involvement.10

Epidermal inclusion cysts consist of stratified epithelium-lined cysts filled with keratin. Trichilemmal cysts are also composed of keratin but lack the granular layer found in epidermal inclusion cysts and are more often found on the scalp. Milia are essentially miniature epidermal inclusion cysts that are also found in eccrine sweat glands. Steatocystoma multiplex are cysts filled with sebum and sebaceous glands.5

Genetics

Lipomas occur in an isolated fashion or as a part of syndromes. The most commonly seen lipomas are typically isolated lesions not associated with any generalized malady. The genetics for lipomas are variable with respect to associated syndromes. With BRRS, there is an association with the MEN1 (Multiple Endocrine Neoplasia 1) and PTEN (Phosphatase and Tensin homolog, deleted on chromosome 10) genes.21,22 These genes are part of the hamartoma tumor syndromes. Other genetic associations with lipomas include 12q14-15, 6p, 13q (for simple lipomas), and 16q and 13q (for spindle cell and pleomorphic lipomas).11 It is commonly accepted that a sarcomatous differentiation occurs in about 1% of simple lipomas.23

Epidermal inclusion cysts have been associated with Gardner syndrome but related entities such as pilar cysts or steatocystoma multiplex are not.24 Leppard25 found that approximately 53% of patients with Gardner syndrome have epidermal inclusion cysts.

Medical Treatment

Historically, treatment of lipomas has consisted of surgical excision, but advances in medical treatment have allowed for reduction in lipoma size. Most treatments have centered on steroid injections to shrink the lipomas. A small case series has shown an approximately 75% reduction in lesion size with 2 to 3 injections of deoxycholate. This is different from prior experience with the commercially available phosphatidylcholine and deoxycholate mixtures used to inject and shrink lipomas.15

Epidermal inclusion cysts will not regress with nonsurgical treatment. However, in cases of infected cysts, some have described infiltration with corticosteroids and delayed surgical excision. This method is not commonly employed.3,25

Surgical Treatment

Surgical treatment of lipomas involves simple excision. In many uncomplicated cases (those without soft tissue infiltration or excessive size), the excision can be performed in the office or the minor procedures room under local anesthetic. The surgical approach involves maintaining the normal aesthetic contours of the skin, however different approaches and incisions are used on the face versus trunk/thigh, and there is debate on whether an elliptical or a punch biopsy incision is more appropriate. It is our recommendation to use an elliptical incision for the most complete excision and best cosmetic outcome.26
After anesthetizing the skin with a local anesthetic, an overlying skin incision is made approximately one half to three quarters the length of the lipoma along Langer lines (defined as parallel skin creases correlating with the direction of least elasticity). It helps to mark the border of the lipoma before dissection. Using a blunt and sharp dissection technique, the fibrous capsule is separated from the surrounding soft tissue. Care must be taken not to invade the capsule to maintain proper aesthetics. Bleeding is controlled with electrocautery. The wound is approximated with absorbable subcutaneous sutures and overlying subcuticular sutures or skin adhesive. The most common postoperative complications include hematomas and seromas, which can be locally managed and usually require aspiration at most.4

Alternative techniques, including minimal-scar segmental extraction of lipomas, have been described for larger/multiple lipomas.4 This technique uses segmental dissection of the lipoma to facilitate removal from a small incision.

Another technique involves liposuction of lipomas if they are found to be histologically benign; however, this technique is not associated with the best aesthetic outcome.27,28 For more advanced tumors involving the deep fascia or muscle, advanced operative planning is required, including imaging with MRI or CT scans.

Several different surgical procedures are used for excision of epidermal inclusion cysts. A small incision is often made over the lesion and the cyst cavity entered to allow expression of the keratin contents. After thorough expression by digital pressure the cyst wall is excised. In contrast to lipomas, a retained cyst wall will more often result in cyst recurrence. As mentioned earlier, there is also a propensity for a significant foreign body reaction if cyst contents are expressed into the surrounding tissues. Bacterial infections can also complicate cyst excision as they make the cyst wall more friable. Common organisms include aerobic and anaerobic flora, specifically Staphylococcus, group A Streptococcus, Escherichia coli, and anaerobes such as Peptostreptococcus and Bacteroides. The cyst wall itself varies in thickness and therefore ease of manipulation and removal depend on the cyst location; facial cysts have thinner walls compared with scalp/body cysts.2,5 Others have described excision via punch biopsies of cysts as large as 1 to 2 cm.26 For more complicated or larger cysts, a wider excision to ensure cyst wall removal is required and therefore is associated with a greater cosmetic defect.

It has been traditionally taught that infected epidermal inclusion cysts should be incised and drained much like an abscess and then later resected, and any surgical intervention should be delayed until after the inflammation subsides. However, more recent studies show that, with primary resection, lavage, and proper wound care, infected cysts can be safely excised with a lower recurrence rate. It awaits further scientific validation before a widespread recommendation to close an incision in an infected field can be adopted.29

The long axis should be along skin lines and the short axis perpendicular to create an elliptical incision. A length to width ratio of 3:1 is used to construct the ellipse. Next, local anesthetic with or without epinephrine is used to form a wheal and anesthetize the skin. A blade is used to enter the dermis but avoid the cyst wall. Using tenotomy scissors, retraction, and blunt dissection, the cyst is removed along with the overlying skin. Care must be taken to ensure hemostasis and that wound closure can proceed with a single layered closure in the cases of small 1- to 2-cm cysts; larger defects will require placement of deep dermal absorbable sutures.30 Infected cysts that are symptomatic can be incised and drained with a small overlying incision and gentle manual evacuation of the cyst contents.

Surgical sites on the face are aesthetically the most important. In planning excision of lesions on the face (lipomas or epidermal inclusion cysts), additional evaluation of
facial furrows along with skin lines should be performed. The facial furrow might preclude a separate larger incision, however the surgeon may be able to place his incision within the furrow in a “distant” fashion and still excise the lesion.31

Trichilemmal cysts (also known as scalp cysts or “wen’s”) are cysts that materialize from the outer root sheath of hair follicles. Their excision is similar to that of epidermal inclusion cysts; however, if a related entity known as a proliferating trichilemmal tumor (PTT) is present, the excision is slightly different. In cases of PTT, a 1-cm margin is used for excision, and these lesions are also appropriate for Mohs procedure.32 Proliferating trichilemmal tumors are larger than trichilemmal cyst counterparts; however, the definitive diagnosis is made during histopathology. Because the correct diagnosis might not be known at the time of the procedure, re-excision might be required to obtain 1-cm margins.

Because malignant skin lesions can be diagnosed grossly as benign, excised lesions should be sent to histopathology. Although this step has fallen out of favor, even experienced surgeons and dermatologists may occasionally classify a malignant lesion as benign. It is therefore advisable to send all biopsied tissues to pathology.33

Recurrence

The local recurrence rate of simple lipomas involving subcutaneous tissue is approximately 1% to 2%.12 There is a general consensus that recurrence of simple lipomas is not affected by wide resection or simply “coring out” the lesion. The risk of local recurrence is greatest with intramuscular lipomas at 19%.5 In the case of well-differentiated liposarcomas, the risk of local recurrence increases with marginal resection, with a reported rate of approximately 50% and a median time postresection of 5 years in patients with marginal resections. Wide resection of well-differentiated liposarcomas decreases the risk of recurrence but is associated with greater morbidity.

The recurrence rate of epidermal inclusion cysts is approximately 3% irrespective of punch biopsy or cyst invasion/expression/excision method, although others have reported a slightly lower rate of recurrence with a wide/elliptical excision.26

Discussion

Simple lipomas can be safely excised under local anesthetic in the surgeon’s office or in the minor procedures room. Although most lipomas are not associated with a malignancy or syndromes states, these should be considered if dealing with children or if there are associated signs of a systemic disorder. Risk of local recurrence is low with most benign lipomas, however more aggressive and deeply rooted lipomas are associated with a significantly higher risk of recurrence. In cases of more advanced lipomas or those with troubling clinical and histologic features, operative planning and imaging are required.

Epidermal inclusion cysts require a more careful dissection to avoid an inflammatory reaction from spilled cyst contents and to decrease the recurrence rate from retained cyst wall. While the decision to perform a surgical excision versus a punch biopsy is dependent on surgeon preference, both techniques have been used successfully in their treatment.

MUSCLE AND NERVE BIOPSIES

Overview

Muscle and nerve biopsies are performed to diagnose inflammatory conditions resulting in myositis and neuropathy (peripheral or systemic). An overview of muscle and
nerve biopsies is presented here, along with indications, contraindications, and technical aspects of the procedures.

Combined muscle and nerve biopsies are performed to diagnose isolated nerve vasculitis (nonsystemic vasculitic neuropathy) and systemic vasculitic neuropathy. Diagnosis has traditionally centered around biopsy of the vastus lateralis or peroneus brevis muscles and sural or superficial peroneal nerves. Recently, it has been shown there is no improved sensitivity in disease detection with combined muscle and nerve biopsies.34

**Indications**

Indications for muscle biopsies include differentiating primary muscular disorders (myopathy) from neurologic disorders (neuropathy), which often present as similar symptoms, and for the diagnosis of systemic immune disorders (Table 1).35

With advancements in genetic analysis, many of the more common “dystrophinopathies” no longer require muscle biopsy as an initial diagnostic mode. These conditions include Duchenne or Becker muscular dystrophy, myotonic dystrophy, periodic paralysis, and endocrine myopathy.

**Tissue Selection and Technique**

Biopsy samples from muscles should be obtained from symptomatic sites. For diffuse conditions, such as systemic vasculitis, the vastus lateralis is chosen. The basic technique of muscle biopsy is as follows.

After drawing an incision along a Langer line, the skin is infiltrated with a local anesthetic of the surgeon’s choice; care should be taken not to inject below the dermis to prevent distortion of tissues. An incision is made along the line and the subcutaneous tissue dissected to the level of the fascia. The fascia is opened and a 1 cm by 0.5 cm by 0.5 cm section of muscle is removed. No monopolar cauterization should be used to prevent damaging the tissue and introducing artifacts in microscopic sections. The bleeding is stopped with digital pressure, packing, and suture ligature if required. The closure is performed in two layers to minimize dead space and prevent seroma accumulation. The skin is closed with absorbable suture in a subcuticular fashion in low-tension areas. The mattress suture is used in high-tension areas such as the shoulder (if a deltoid biopsy was performed).

Three samples should be obtained during the biopsy for fresh, fixed, and genetic/biochemical analysis. The amount of muscle removed can vary depending on whether the biopsy is being performed as an open procedure or a core needle biopsy. During the open procedure, samples approximately 1 cm long and 0.5 cm by 0.5 cm wide are obtained. In a core needle biopsy, the core size varies depending on the needle and is

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<th>Indications</th>
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<td>Inflammatory myopathy</td>
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<td>Steroid induced myopathy</td>
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<td>Metabolic myopathy</td>
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<td>Limb girdle</td>
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<td>Periodic paralysis</td>
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<td>Endocrine myopathy</td>
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really only useful for biochemical markers and genetic analysis, without yielding significant morphologic tissue data.

Once the fresh sample is obtained, it is rushed to the laboratory using an ice-chilled bag on saline soaked gauze. A light microscopy slide is made from the fresh sample and the tissue stained with hematoxylin and eosin. Alternate stains to isolate proper protein production and function are outlined in Table 2.

The fixed (permanent) sample is used for electron microscopy and involves tissue that is approximately the same size as used in the fresh (frozen) section. The sample is stored in 4% paraformaldehyde and then subsequently immersed in gluteraldehyde.

Electron microscopy (EM) is a costly method to evaluate cellular structures at the molecular level. During the original muscle biopsy, a sample should be kept from the permanent section for EM. The process of fixation and preparation of EM samples is beyond the scope of this article but the initial steps are similar to fixation of the permanent sample.35

Findings and Follow-up

Muscle biopsies can also provide information to distinguish between primary neuropathies and myopathies. Primary neuropathies consist of nerve atrophy from numerous causes.

There are certain microscopic features that can help to distinguish a peripheral neuropathy from a myopathy including evidence of individual muscle fiber atrophy, regrouping of muscle fibers, reparation, and denervation.

The diagnosis of myopathies is only partly dependent on the tissue biopsy. At present there are numerous tests that can diagnose individual myopathies, including tests for Duchenne, Becker, and mitochondrial muscular dystrophies.

Findings of inflammation, helpful in the diagnosis of myositis, can also be present on the muscle biopsy.

Indications for Nerve Biopsy

Nerve biopsy is indicated in the diagnosis of treatable vasculitic conditions and if the disease being diagnosed is associated with neuropathic features; biopsy of the sural nerve is frequently carried out.36

As with muscle biopsies, there are many other tools used to establish the diagnosis of neurologic conditions without relying on a tissue sample, including nerve

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<td>Basophilic and eosinophilic cell structures</td>
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<td>NADH</td>
<td>Mitochondria and endoplasmic reticulum</td>
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<td>Fiber specific</td>
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conduction velocity, electromyography, and autonomic and sensory studies. The analysis and description of these studies is beyond the scope of this article.

**Nerve Biopsy Technique**

As with muscle biopsy, a biopsy of the symptomatic nerve should be taken; sometimes this is a sensory nerve, other times a motor nerve. In the case of a sensory nerve, a segment can be resected and the patient might have recovery of some sensory function. For motor nerve biopsies, each nerve bundle is tested with electric stimulation to see if it has motor function; the bundle that does not cause muscle contraction is resected. As with a sensory nerve biopsy, there might be some sensory loss that resolves with time.

The biopsy of the sural nerve is explained here. The sural nerve is an easily accessible peripheral nerve commonly associated with sensory neuropathies. Its natural course is between the lateral malleolus and the Achilles tendon. The lesser saphenous vein also courses just lateral to the sural nerve and compression along the proximal leg will cause the vein to distend. After the landmarks are identified, the region is infiltrated with a local anesthetic. Next, a 2- to 3-cm incision is made between the fibula and the Achilles tendon. The subcutaneous tissue is then dissected bluntly and sharply. Care is taken to avoid damaging the nerve and therefore bipolar cautery is used instead of monopolar cautery due to decreased likelihood of thermal injury. The nerve is dissected away from the lesser saphenous vein in a careful manner.36

If diffuse neuropathy is suspected a fascicular nerve biopsy should be taken; in the case of neuropathy of a patchy distribution, a whole nerve biopsy is needed. The biopsy specimen is attached to a small gauge needle and suspended in fixative. Care must be taken to avoid physical manipulation of the nerve and the needle suspension prevents the nerve from contracting/coiling.36

The skin is then closed in the usual two-layered closure with a deep dermal absorbable suture and a mattress nonabsorbable skin suture.

**Nerve Biopsy Complications**

The most common complications of a peripheral sensory nerve biopsy are allodynia, anesthesia, and paresthesias. These are seemingly related to the length of the nerve resection and will resolve over time (most within the first 18 months postsurgery). The degree of systemic neuropathic disease, such as diabetes mellitus, will correspond to the duration of neuropathic pain.

Other complications of nerve biopsies include local wound issues such as infection and wound breakdown, which occur less than 20% of the time.36

**Discussion**

Muscle and nerve biopsies are used for the diagnosis of a variety of medical problems. Although there are other genetic and biochemical markers now available that can diagnose diseases previously proven by biopsy, these surgical techniques still have appropriate uses. Although the procedures are straightforward, there are important technical issues to assist in getting the best specimen to avoid confounding disease diagnosis.

**REFERENCES**