

1. REVIEW OF LITERATURE

1.1. Lipoma

Lipomas are benign neoplasms of mesenchymal origin composed of mature adipose tissue. They are the most common benign form of soft tissue tumors.⁽¹⁾ These slow-growing benign tumors are usually non-painful. Lipomas are rarely life-threatening.⁽²⁾ However, lipomas growing in internal organs can be more dangerous. For instance, lipomas in the gastrointestinal tract can cause obstructions. Thus can be considered "*malignant by location*", despite being a benign growth histologically.⁽³⁾ Rarely, lipomas may be associated with syndromes such as hereditary multiple lipomatosis, adiposis dolorosa, Gardner's syndrome, and Madelung's disease.⁽²⁾ There are also variants such as angioliomas (lipoma containing vascular structures, usually painful);⁽⁴⁾ spindle cell lipomas (consisting of adipocytes, spindle cells and collagen fiber, found subcutaneously in the back, shoulders and neck), and adenoliomas (composed of both glandular and adipose tissues, e.g. in sweat glands).⁽²⁾

Histopathology of lipomas shows mature adipose tissue, without evidence of malignancy or dedifferentiation. Cells appear large, regular, polygonal, reticulated, and optically empty with delicate cytoplasmic membranes and unremarkable, eccentric nuclei consistent with mature fat. Macroscopically, they are soft, yellow, fusiform tumors, with indistinct intra-parenchymal margins.⁽⁵⁾ Lipomas must be distinguished from liposarcoma, which is a malignant tumor that arises in fat cells in deep soft tissue and can have a similar appearance. Indeed, magnetic resonance imaging (MRI)⁽⁶⁾, plain X-ray⁽⁷⁾ and sonography⁽⁸⁾ are used for the initial screening of the location of lipomas but the investigation of choice is the MRI scan as it provides accurate details of the lesion and surrounding anatomy, which is vital in the preoperative assessment of patients.^(6, 7) However, these imaging techniques cannot differentiate between lipomas and liposarcoma. Histopathological examination of fine-needle aspiration biopsy and the excised mass after surgery is considered the mainstay for differentiation between lipomas and liposarcomas^(9, 10). It is worth noting that the malignant transformation of lipomas into liposarcomas is usually very rare.^(11, 12)

Lipomas have been identified in all age groups. However, they are most common in middle age between 40 and 60 years of age.⁽²⁾ However, congenital lipomas such as congenital intraspinal lipomas have been also reported in children.⁽¹³⁾ For instance, lipoma of the *conus medullaris*, the tapered lower end of the spinal cord (lipomyelomeningocele), occurs in approximately one in 4000 births in the United States of America and females are at increased risk (prevalence female/male ratio 1.5:1). Lipomas are usually relatively small with diameters of about 1–3 cm, but in rare cases they can grow over several years into "giant lipomas" that may weigh up to 4–5 kg.⁽¹⁴⁾

The causes for the development of lipomas are diverse and ambiguous. Studies demonstrated a hereditary component in the tendency to develop some types of lipomas such as familial multiple lipomatosis.⁽¹⁵⁾ Alternatively, alterations of fat metabolism induced by corticosteroid excess can play a role in the development of some cases of

lipomas.⁽¹⁶⁾ For example, in 2000, Agraharkar and coworkers reported the first case of growth of intramedullary lipoma in a renal transplant recipient after steroid use. Also, cases have been reported where minor injuries are alleged to have triggered the growth of lipomas. In such setting these are called "*post-traumatic lipomas*".⁽¹⁷⁾ However, the link between trauma and the development of lipomas is still controversial.⁽¹⁸⁾ Although obesity is not a direct cause for lipoma, however, it usually complicates the prognosis of lipomas.^(19, 20) Therefore, patients in whom the spinal cord lipoma is only partially resected should be informed that substantial weight gain or pregnancy may aggravate their symptoms.^(21, 22)

Lipomas can be classified according to their location into superficial subcutaneous lipomas and deep lipomas. Superficial subcutaneous lipomas are the most common type of lipomas. They lie just below the surface of the skin. They occur mostly in the trunk, thigh, and forearm, or anywhere in the body where fat is located such as the head and neck.^(23, 24) On the other hand, deep lipomas comprise (i) intramuscular and intermuscular lipomas, (ii) tendon sheath lipoma, (iii) brain and spinal cord lipomas and (iv) intra-neural and peri-neural fibrolipoma.⁽²⁵⁾

Studies showed that intramuscular lipomas are located within the skeletal muscles. They may be circumscribed or infiltrative. Alternatively, intermuscular lipomas are located between the skeletal muscles and are usually circumscribed.⁽²⁶⁻²⁸⁾ Intramuscular and intermuscular lipomas are mostly present in the extremities.⁽²⁹⁾ However, they may also be present in any other muscles such as the chest wall,⁽³⁰⁾ the tongue,⁽³¹⁾ the eye lid,⁽³²⁾ or infiltrating in the paraspinal muscles.⁽³³⁾

On the other hand, tendon sheath lipoma is considered a rare condition. It is a lipoma adherent to tendon or intersecting its fibers. It is usually found in tendons of hands and wrist and less often in ankle and foot.^(34, 35) Previous reports suggested that tendon sheath lipoma may be considered as a variant of lipoma arborescens, a rare condition affecting synovial linings of the joints and bursae, with "*frond like*" i.e. palm leaf-like depositions of fatty tissue.⁽³⁶⁾ Though benign, the consequences of tendon sheath lipoma might be serious. For instance, tendon sheath lipoma was reported to be associated with quadriceps tendon rupture.⁽³⁷⁾ Carpal tunnel syndrome caused by flexor tendon sheath lipoma is considered another example for the undesirable outcome of such lipomas.⁽³⁸⁾

Intracranial lipomas are rare congenital malformations. Most brain lipomas are located at midline. These tumors are slow growing and have favorable outcome. However, if they became symptomatic, seizures are the most common symptom.⁽³⁹⁾ On the other hand, spinal cord lipomas are rare lesions that constitute less than 1% of all intra-spinal tumors. Spinal lipomas typically consist of normal mature adipocytes separated into clusters by numerous collagen bands (due to abundant fibrous tissue it is often referred to as fibrolipoma); in addition they may contain other tissues e.g. nerves or striated muscles.⁽⁴⁰⁾

Spinal cord lipoma may take place in different locations along the spinal cord. The historic classification of spine tumors based on the use of myelography is: (1) extradural extramedullary, (2) intradural extramedullary and (3) intradural intramedullary.⁽⁴¹⁾ Most isolated spinal cord lipomas are intradural extramedullary. True intramedullary lipomas are rare. The prognosis for intramedullary lipomas is worse than

for extra-medullary lipomas or lipomas associated with the *conus medullaris* or *cauda equine*.⁽⁴²⁾

Spinal cord lipoma may be associated with *Spina Bifida*, where some vertebrae overlying the spinal cord are not fully formed and remain unfused and open due to congenital disorder caused by the incomplete closing of the embryonic neural tube. Studies showed that spinal cord lipomas that are not associated with *Spina Bifida* are rare and most commonly located within the thoracic spinal cord. They may be symptomatic but more commonly present in adulthood.⁽⁴³⁾ Alternatively, most spinal cord lipomas are associated with spinal dysraphism and patients with dysraphism usually have sacral or lumbosacral defects associated with a subcutaneous lipoma.⁽⁴²⁾

Spinal cord lipomas seem to have a peak presentation between 10 and 40 years, with a slight male preponderance. The symptoms of spinal cord lipomas are related to mass effect and secondary compressive myelopathy.⁽⁴³⁾ Intra-spinal lipomas are frequently responsible for progressive pain and neurological deficits affecting sphincter, motor and sensory functions due to distortion or compression of the nervous system.⁽⁴⁴⁾ This compression can lead to sensory changes (numbness, tingling), weakness, difficulty with urinating or with bowel movements, incontinence, and spasticity (stiffness) of the extremities.^(43, 45) The patient is usually presented with a long indolent history, followed by a dramatic worsening over months. All patients describe local back pain in the region of the lipoma. Also, paraparesis, sensory disturbance, gait difficulties and incoordination may be present. These symptoms vary in location depending on the tumor site. One or more of these symptoms is always present and may prompt the patient to seek medical attention. It is postulated that slow growth of the lipoma allows accommodation within the spinal canal without compromise of function, until a point is reached where further growth causes a rapid decline in function.^(43, 46)

Lipoma of the *conus medullaris* (lipomyelomenigocele) is a congenital lesion that is associated with *Spina Bifida* (congenital failure of closure of the spinal bones). It is associated with abnormal fat accumulation that starts below the level of the skin and extends through the bony opening to the spinal cord. The lesion itself is composed of a descended *conus medullaris* infiltrated by fat, which emerges as a skin-covered subcutaneous mass that is usually found in the lumbosacral region. Lipomyelomenigocele is diagnosed in children because of the presence of a cutaneous marker or fatty mass; however, the diagnosis of underlying spinal dysraphism (defective fusion of the raphe i.e. the seam line of the neural tube) is usually missed. This problem is not diagnosed until adulthood when back pain or a progressive neurological deficit calls attention to the problem.⁽⁴⁷⁾ Indeed, spinal cord lipoma without spinal dysraphism is a rare condition.^(48, 49) Lipomyelomenigocele is a common cause of the tethered cord syndrome⁽⁴³⁾ that might require surgery.⁽⁵⁰⁾

Because more than 90% of patients will have an obvious subcutaneous soft tissue swelling over the lumbosacral region of the spine, and in one-half to two-thirds of patients the lump can be quite bulky, families seek medical advice for cosmetic reasons. Neurological function most frequently is intact at birth but insidious deterioration increases with age. The clinical manifestations are those of the 'tethered cord syndrome' which include vertebral anomalies (e.g. *Spina Bifida*), cutaneous (dermal sinus tract and dimple in the spine range, and focal hirsutism), orthopedic abnormalities (limb

abnormalities and scoliosis i.e. obliquity and bending of the vertebral column), neurological deterioration (bowel and bladder dysfunction), and anorectal malformations.⁽⁵¹⁾ Some patients remain asymptomatic until adulthood when they develop progressive symptoms and signs This usually takes place following a sudden movement which causes traction on the spinal cord (e.g. bending and accidents); in these patients pain is the usual presenting feature and this is a major difference between adult and pediatric presentations.⁽⁵²⁾

The *filum terminale* (terminal thread), is a delicate strand of fibrous tissue, about 20 cm in length, proceeding downward from the apex of the *conus medullaris*. It is one of the modifications of pia mater. It gives longitudinal support to the spinal cord. Unlike lipomyelomenigocele, lipoma of the terminal filum (fatty filum) is an occult condition where no cutaneous anomalies or subcutaneous collections are present to indicate an underlying problem. Fatty filum is also associated with the tethered cord syndrome. Indeed, surgical treatment of filum lipomas carries significantly lower risk than that for lipomas of the *conus medullaris*. The goal of surgery is to disrupt the connection between the abnormal fibrofatty tissue and the underlying spinal cord.⁽⁴³⁾

Intradural spinal lipomas are most commonly found in the thoracic region in adults, whereas in children the cervical spine appears to be the most common site.⁽⁵³⁾ Intradural spinal lipomas are fatty accumulations that are completely intradural, have no subcutaneous component, and manifest symptoms when they become large enough to have mass effect.^(54, 55) Alternatively, epidural lipomatosis occurs when excessive amounts of epidural fat are synthesized e.g. in a patient receiving exogenous steroid agents or cases of severe obesity. The excessive fat exerts mass effect on the underlying neural structures and can cause a compressive myelopathy or *cauda equina* syndrome. Chronic lipomatosis is usually treated with weight loss or discontinuation of steroids. It rarely requires decompressive surgery.⁽⁴³⁾ It is worth noting that extradural angiolipomas may rarely appear in the spine and extend to the brain.^(43, 56)

Neural fibrolipoma is an overgrowth of fibro-fatty tissue along a nerve trunk that often leads to nerve compression. It most commonly occurs in the upper extremity in infants and children, usually affecting the median nerve. However, it might in some rare cases affect other sites such as the foot^(57, 58) the neck⁽⁵⁹⁾ or the tongue.⁽⁶⁰⁾ The fibro-fatty tissue may proliferate around the nerve and infiltrates the epineurium and perineurium.⁽⁶¹⁾ One-third of the cases of neural fibrolipomas are associated with enlargement of one or several digits of hands or feet, diminished sensation, paraesthesias (sensation of tingling, tickling and prickling) and compression neuropathy.^(62, 63) In 2012, Missori and co-workers described a case in which neural fibrolipoma caused spinal cord compression syndrome. In that case, the neural fibrolipoma originated in the thoracic nerve at the T6-7 extradural level in the left conjugate foramen and extended into the thoracic cavity. The following photos show different types of lipoma (Figure 1-5).

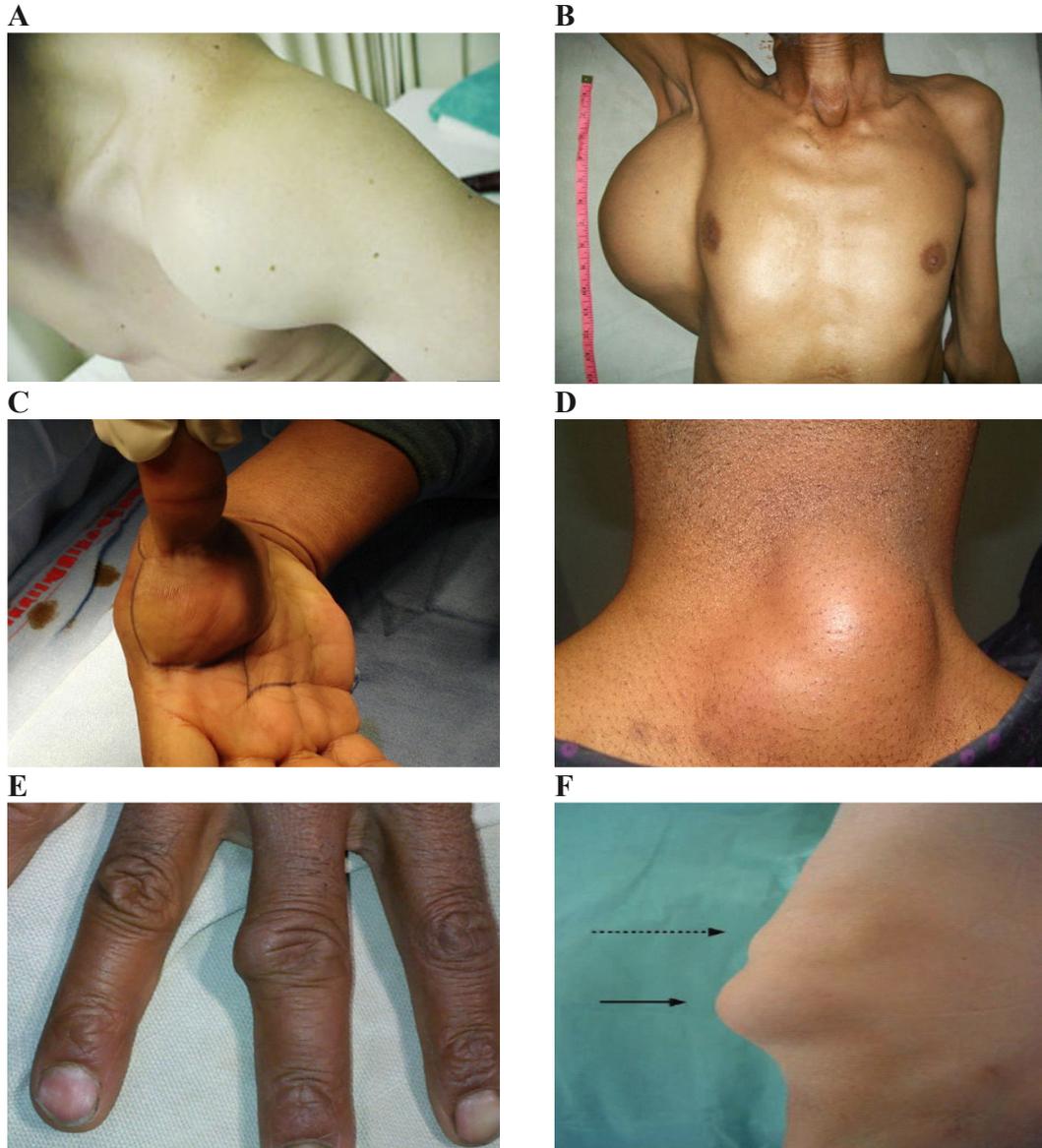


Figure 1: Photos showing clinical views of some of the sites for the development lipomas. (A) lipoma at the shoulder.⁽⁶⁴⁾ (B) giant axillary lipoma.⁽⁶⁵⁾ (C) lipoma in the hand.⁽⁶⁶⁾ (D) neck lipoma. (E) lipoma of the middle finger.⁽⁶⁷⁾ (F) intrapatellar ligament lipoma.⁽⁶⁸⁾

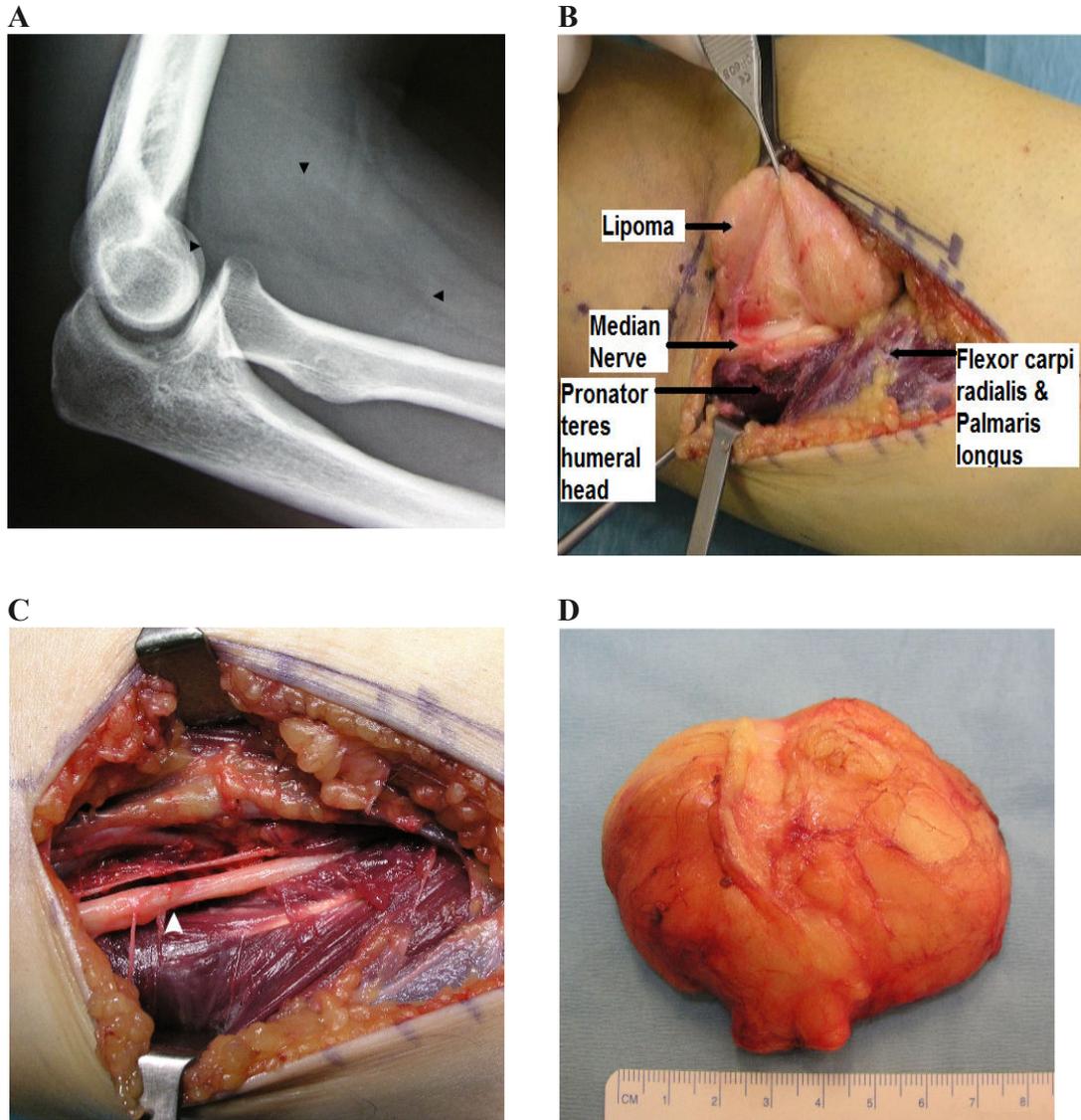


Figure 2: Photos showing compression of the median nerve in the proximal forearm by a giant lipoma. (A) A lateral elbow X-ray subtly demonstrates a well circumscribed mass in the anterior proximal forearm (arrows). (B) Intraoperative photo showing the median nerve within the intermuscular lipoma. (C) Surgical area after lipoma excision: the arrow shows the hour-glass deformation of the nerve at the level of the compression. (D) The giant lipoma was excised completely and measured 8 cm × 6 cm × 3 cm.⁽⁶⁹⁾

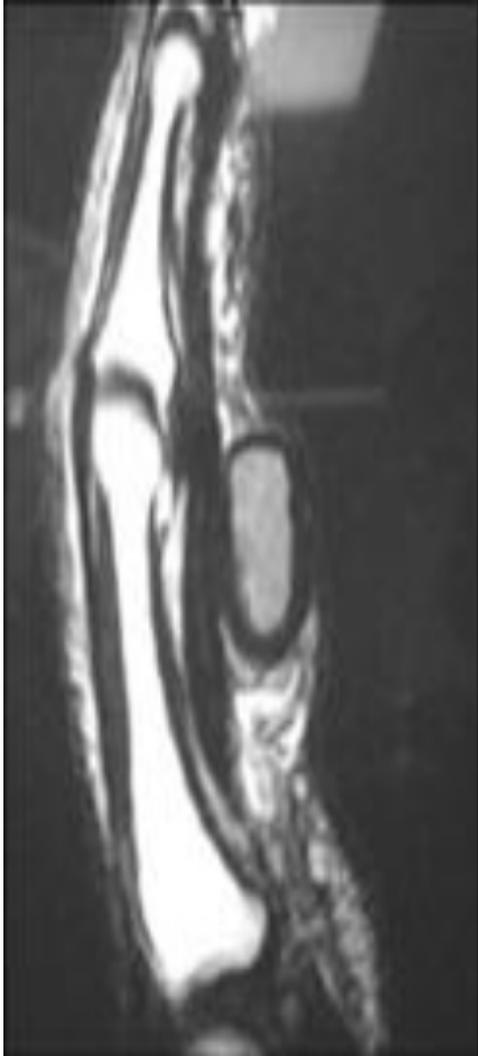
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Figure 3: Photos showing lipoma of the index finger. (A) MRI T1 sequence, sagittal image of the lipoma and its attachment to the tendon sheath. (B) Lipoma arises from the subcutaneous tissues of proximal phalanx of the right first digit. (C) Removal of the tumor including the extensions into the tendon sheath.⁽⁷⁰⁾

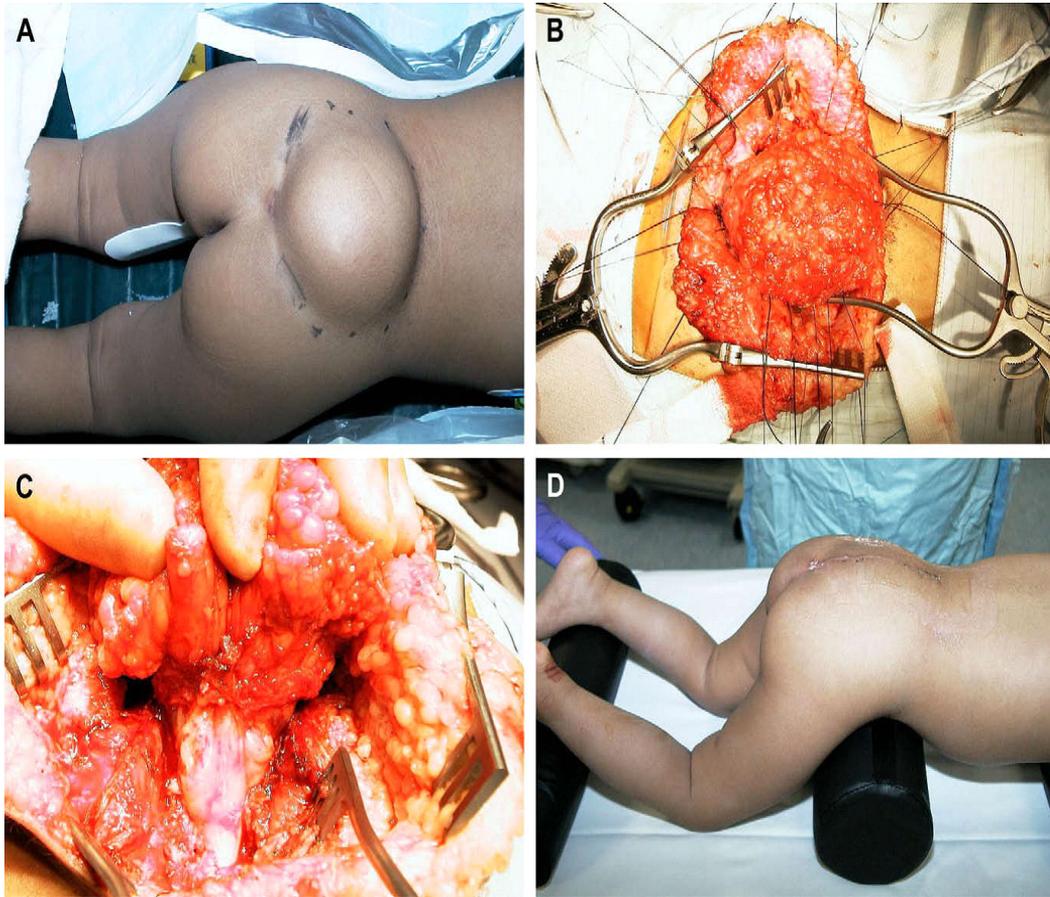


Figure 4: Photos showing typical case of spinal lipoma undergoing primary surgery. (A) Preoperative view. (B) The lipomatous mass is dissected all around. (C) Interface between the lipoma and spinal cord. (D) Postoperative view.⁽⁴³⁾

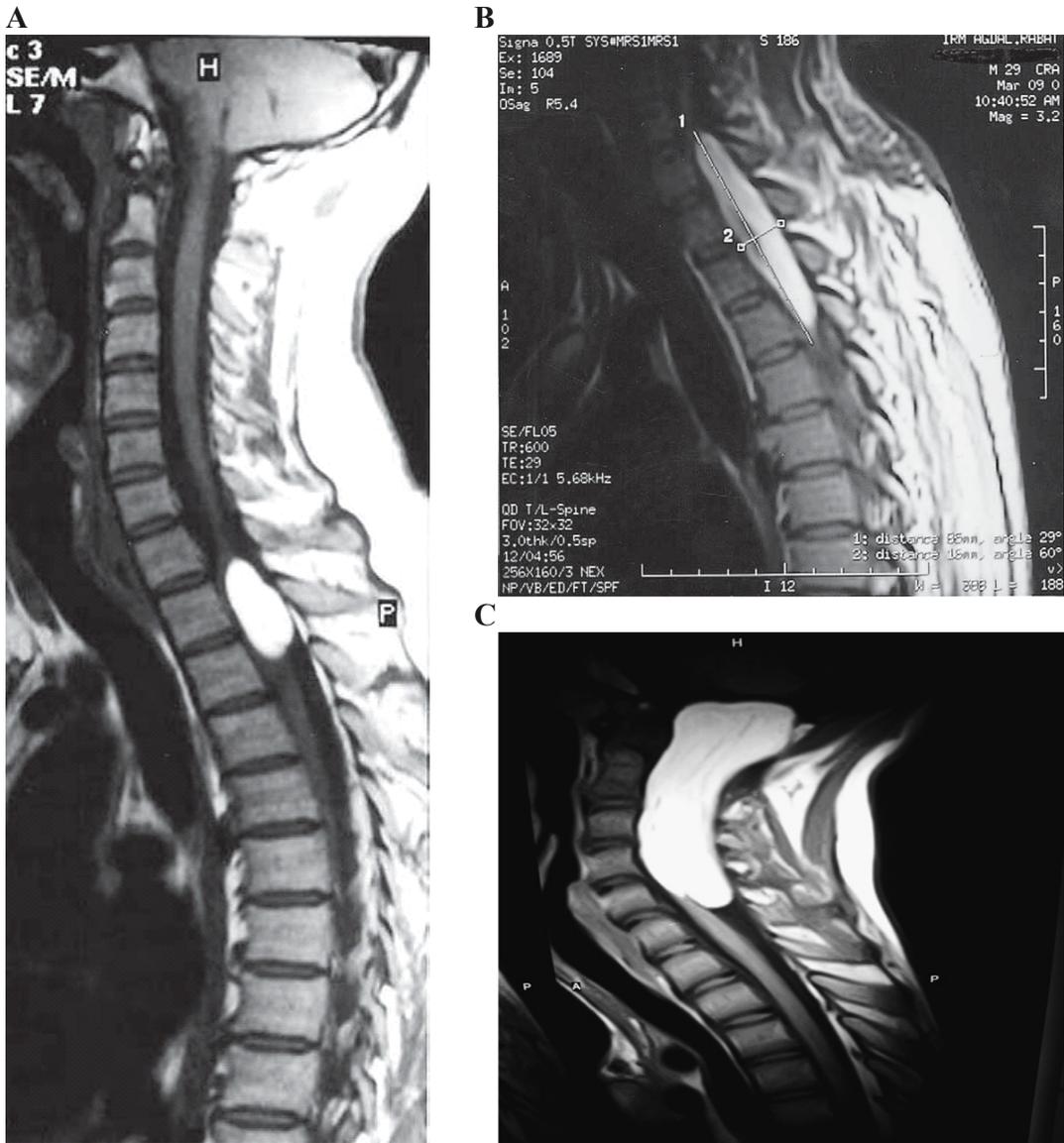


Figure 5: MRI showing spinal cord lipomas. (A) T1-weighted sagittal image showing well defined ovoid intra-dural lesion at T2/3 level. The high signal intensity is consistent with fat.⁽⁴²⁾ (B) T1-weighted noncontrast-enhanced image, sagittal view showing increased signal intensity of intramedullary lipoma extending from C6 to T4.⁽⁴⁸⁾ (C) T1-weighted sagittal image showing massive lipoma extending from the cervicomedullary junction to the C6 level.⁽⁷¹⁾

1.2. Surgical excision of lipoma

Most lipomas are best left alone, but rapidly growing or painful lipomas can be treated with a variety of procedures ranging from steroid injections to excision of the tumor. Studies showed that deep lipomas have a greater tendency to recur than superficial lipomas, because complete surgical removal of deep lipomas is not always possible.⁽⁷²⁾

Because most patients, in cases of superficial lipomas, seek medical care for cosmetic reasons; surgeries with minimal invasive techniques are recommended, especially in the face and neck. Minimally invasive endoscopic surgery for removal face and neck lipomas were first reported by Gagner in 1996. Using more advanced endoscopic techniques, various complications, such as injury to nerves and vessels, are prevented and cosmetically satisfying results were obtained along with decreased operating time and hospital stay.⁽⁷³⁾ For deep lipomas, the choice between endoscopy and surgical excision is a matter of debate. For instance, in cases of endobronchial lipoma, when a benign tumor is suspected, endoscopic resection is the treatment of choice, which allows histological diagnosis and in the same time a definitive therapy with resolution of symptoms. Alternatively, surgical option is reserved for the not certainly determined benign or malignant lesions.⁽⁷⁴⁾

Surgical treatment of intra-spinal lipomas consists of untethering of the cord in symptomatic cases with de-bulking of the lipomatous component to improve the spinal contour.⁽⁷⁵⁾ However, the often extensive nature of intra-spinal lipomas and their complex relationship to neural elements can make spinal cord untethering difficult to achieve.⁽⁷¹⁾ The overwhelming neurosurgical opinion regarding treatment of spinal cord lipoma is that surgical de-bulking of the tumor is the goal, and not total excision.^(53, 76) Although total surgical excision of spinal cord lipoma are sometimes performed,⁽⁷⁷⁾ it has generally shown less post-operative improvement, and in some cases significant worsening of symptoms compared to partial de-bulking of lipoma.^(50, 78) Notably, long-term follow-up is needed, and repeat de-bulking of the lipoma is indicated if there is an increase in tumor size due to hyperplasia of residual adipocytes, when tumor growth is associated with neurological deterioration.⁽⁷⁸⁾ Despite the fact that localized back pain is often reduced following de-bulking of spinal cord lipomas, the neurological function is largely unchanged, and in some patients it becomes even worse. This may be due to the congenital nature of the many spinal cord lipomas replacing neural tissue during embryonic development, so fewer redundant spinal tracts form, and thus there is less physiological reserve of the spinal cord.^(79, 80) Therefore, early surgical de-bulking of the lipoma prior to permanent spinal cord injury might prevent the irreversible spinal cord dysfunction seen in many cases.⁽⁸¹⁾

The role of surgery in treating spinal cord lipomas is to stabilize the patient's clinical course. However, separating the tumor might compromise the vascularity of the cord. It is believed that a slice of tumor must be left over the cord in order to prevent vascular insult. Indeed, aggressive attempts at excision or cord handling must be avoided.⁽⁸²⁾ The lipomatous element is firmer in consistency than the adjacent cord and therefore when attempting to separate the tumor from the adjacent cord, there is a significant likelihood of damaging the underlying cord. It is extremely important that surgical resection margins remain within the lipomatous tumor at all times. Creating a

plane of cleavage between the tumor and cord, though sometimes tempting, will produce excessive handling and vascular insult to the cord.⁽⁸³⁾ Also, the normal cord structures must not be exposed to the heat of bipolar coagulation. The use of bipolar coagulation should be kept to a minimum and it should be used strictly for the tumor vessels. The heat produced during bipolar coagulation will therefore dissipate only in to the surrounding lipoma and not to the normal cord structures. Moreover, vessels around the lipoma should be left untouched. Nonetheless, sufficient de-bulking of the tumor must be achieved to ensure a long-term favorable outcome.^(53, 83)

Truly, the mainstay treatment for lipomas is usually surgical partial or complete excision according to the lipoma size and location. However, despite the careful attention of surgeons and staff during operation, many studies have reported significant rates of postoperative wound complications including wound infections and wound breakdown.^(43, 84) Technical developments including improved operating microscopes, better illumination, improved microsurgical instruments, refined lasers, and advances in intraoperative monitoring have all contributed to surgery-related advances. However, the risk of surgery-related neurological deterioration following surgical removal of lipomas can limit the surgical approach.^(40, 43) This is of particular importance in cases of spinal cord lipomas and lipomas adjacent to critical nerves. In cases of spinal cord lipomas, complications may extend to cerebrospinal fluid (CSF) leakage and subcutaneous pseudomeningocele (abnormal collection of CSF in cavities between soft tissue),⁽⁴⁴⁾ which places another challenge in the management of intra-spinal lipomas. Because of these complications, the treatment of these lesions has generated much controversy, with some physicians supporting surgical treatment for all patients regardless of symptoms and others proposing that surgery be withheld until symptoms develop.⁽⁸⁵⁾

1.3. Injection lipolysis

In 1976, Pistor hypothesized that injections of numerous medications into various levels of the skin could maximize their therapeutic effects locally; while significantly reduce their adverse effects systemically. This was applied later clinically for pain relief in dental care and musculoskeletal diseases, where local injections of anesthetics, anti-inflammatory and vasodilators became standard regimens.⁽⁸⁶⁾ For example, triamcinolone was injected intralesional by dermatologists for numerous inflammatory conditions.⁽⁸⁷⁾ Other applications also emerged where many pharmacologically active substances such as hyaluronic acid and botulinum toxin were injected locally in the skin for cosmetic improvement. Such procedures were labeled as “*Mesotherapy*”.⁽⁸⁷⁻⁸⁹⁾

On the other hand, injection lipolysis, also known as “*lipodissolve*,” refers to a procedure in which drug mixtures are injected into patients with the goal of breaking down small deposits of localized fat.^(90, 91) In the past years, the use of injection lipolysis has increased and became the most economically used technique to reduce local fat. It is considered a good adjunct or alternative for those patients seeking minimally invasive treatment.^(90, 92) In lipodissolve, phosphatidyl choline (PC), a natural phospholipid, and deoxycholate (DC), a natural emulsifier, are the most commonly used drugs.⁽⁹²⁾

Injection lipolysis is commonly confused with mesotherapy. For this reason, treatment with PC/DC has been mislabeled as mesotherapy for years.⁽⁸⁹⁾ Although mesotherapy can also be used to dissolve fat, injection lipolysis targets deeper layers in the skin. For dissolving fats with mesotherapy, vitamins, minerals and different drugs are injected two to four millimeters from the surface of the skin. This is often employed to improve the surface of the skin, to smooth the appearance of cellulite and to improve the texture of the skin, and may also be used to complement injection lipolysis procedures.^(89, 93) However, in the area of fats dissolution, PC/DC injection lipolysis has been more rigorously investigated than traditional mesotherapy and may have significant potential to treat localized collections of adipose tissue^(86, 93) and lipomas.⁽⁹⁴⁾

Deoxycholic acid (DC) is a natural emulsifier and a secondary bile acid that results from the metabolism of a primary bile acid called cholic acid by the intestinal bacteria.⁽⁹⁵⁾ On the other hand, phosphatidylcholines (PCs) are a class of phospholipids that incorporate choline. They are major component of biological membranes and can be easily obtained from a variety of readily available sources such as egg yolk or soy beans. PCs are insoluble in water, and thus require an emulsifier, traditionally DC, to solubilize them.^(96, 97)

Advances in knowledge regarding the efficacy and mechanism of action of both PC and DC have been achieved mainly in Germany because most users are found in Germany when compared on an international level. The reason for this is that the combination of PC and DC as active substances has been approved for i.v. treatment of fat embolisms in Germany⁽⁹⁸⁾ and hyper-lipoproteinemia.⁽⁹⁹⁾ It is thus readily available, but the subcutaneous injection of the drug Lipostabil N® is considered as off-label use.⁽⁸⁸⁾

Although not yet Food and Drug Administration (FDA)-approved,⁽⁹⁰⁾ injection of PC/DC preparation is now widely used as an alternative to liposuction for the reduction of subcutaneous fat. In 2003, Rittes and co-workers reported on a new office procedure

using PC/DC for correction of localized superficial fat deposits. The procedure was applied in 50 patients by injection of 5 ml (250 mg/5 ml) of PC into the fats using insulin needle. The reduction in fats remained without recurrence over a 2-year follow-up period (Figure 6). Although not as dramatic as liposuction, the results from these studies suggest that these relatively easily performed injections may be effective at reducing small collections of fat.⁽¹⁰⁰⁾

A recent experimental study performed on dogs showed that PC can decrease intra-peritoneal fat (visceral adipose tissue). Reduction of this fat is aesthetically and functionally desirable because it poses significant metabolic risks. The use of single application of PC produced no intra-peritoneal abscesses or adhesions, and there was no injury to any intra-abdominal organs, which can be promising for further trials in humans.⁽¹⁰¹⁾ Similarly, clinical application of injection lipolysis and hyaluronic acid dermal filler in rejuvenation of the lower face showed promising short-term results.⁽¹⁰²⁾ Other reports described the use of PC/DC formulations for buffalo hump,⁽¹⁰³⁾ and double chin fat⁽¹⁰⁴⁾ in humans with no significant systemic or organ-specific toxicity. Notably, in 2011, Nanda reported a case of 35-year-old healthy male with complaints of a gradually increasing growth on right wrist. The over growth was identified as lipoma. This case was successfully treated with PC/DC injection lipolysis. Although the injections were not perceived as painful by the patient, immediately after the injections there was swelling, redness and burning sensation which persisted for around half an hour after the injection. The patient remained under follow up for the following 9 months with no evidence of any recurrence of the lipoma (Figure 7).

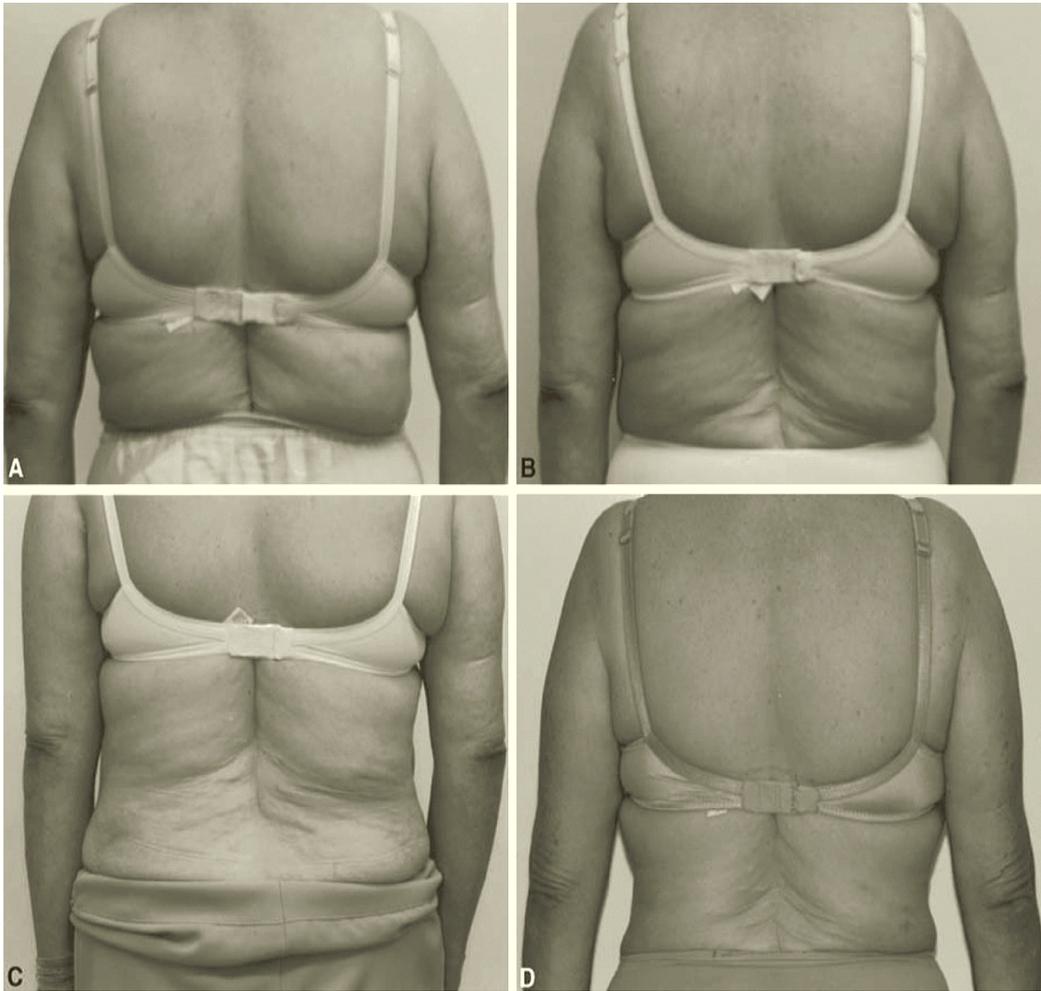


Figure 6: Photos showing injection lipolysis used for aesthetic contouring (A) 57-year-old woman with local fat deposit because of cortisone use before procedure. (B) After two applications of phosphatidylcholine (PC; 30 days). (C) After four applications of phosphatidylcholine (60 days). (D) After eight applications of phosphatidyl choline (120 days).⁽¹⁰⁵⁾

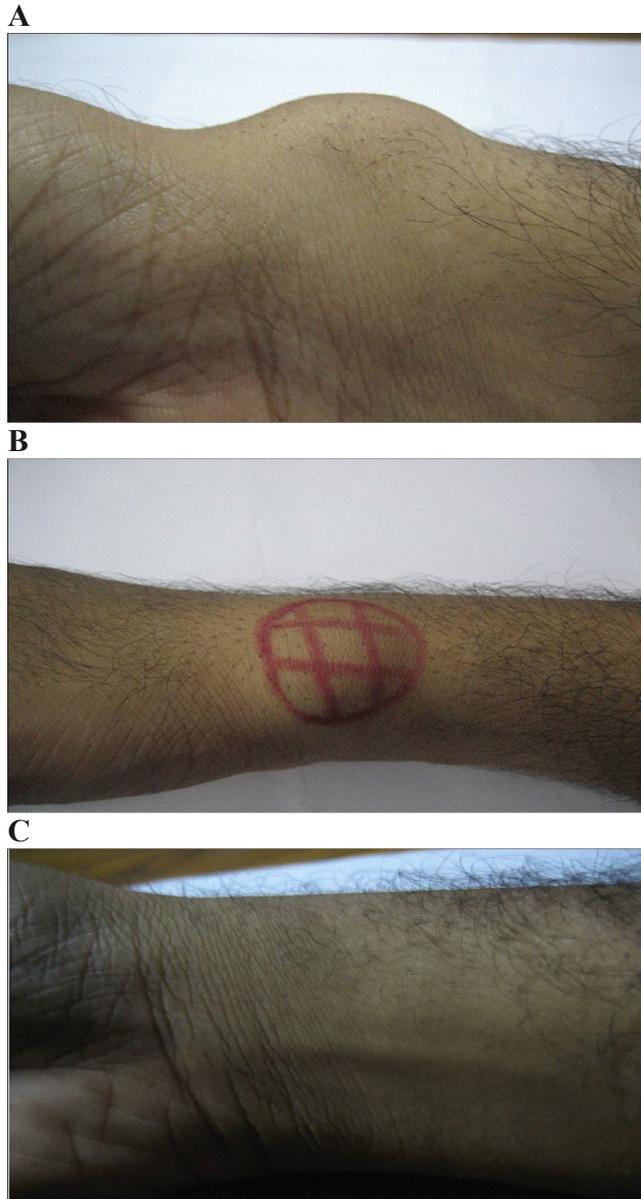


Figure 7: Photos showing injection lipolysis for lipoma at the wrist. (A) The lesion was cleaned. (B) The area was divided into small grids (1.5 cm apart). Solution of phosphatidyl choline (PC) and deoxycholate (DC) was filled in insulin syringes. The pinch and pull technique was used. The lipoma was pulled away from the underlying structures and injected in each of grids. Care was taken not to inject any material while withdrawing the needle to avoid any intradermal deposition of the drug. (C) In the next 48 h, the lesion shrunk to half of its original size and disappeared completely within next 3 weeks, after the first injection.⁽⁹⁴⁾

Many clinical studies have reported that the subcutaneous injection of PC formulation reduces fat.⁽¹⁾ Although the biochemical mechanisms are very poorly studied,⁽¹⁰⁶⁾ it has been suggested that no enzymatic lipolytic pathway is involved.⁽¹⁰⁷⁾ Thus, it is thought that the PC/DC formulation dissolves local fat deposits in a nonspecific manner.⁽⁹¹⁾ PC is a lecithin-derived phospholipid, which is widely-distributed in human cell membranes. Increased PC in cell membranes can accelerate lipolysis by improving sensitivity to insulin.⁽¹⁰⁸⁾ Studies performed on 3T3-L1 cell line, which are mice adipocytes sensitive to lipogenic and lipolytic hormones including epinephrine, isoproterenol and insulin⁽¹⁰⁹⁾ also highlight an apoptotic effect of PC on adipocytes.⁽¹¹⁰⁾ However, studies had failed to prove lipolytic activity for PC.⁽¹¹¹⁾ On the other hand, DC, being an emulsifier, is implicated in nonspecific fat lysis causing fat dissolution.⁽¹¹²⁾

Even though injection lipolysis using PC/DC is considered generally safe and free of complications, there have been rare reports on poor results, edema, pain, hematoma, infection or localized skin and tissue necrosis. Because injection lipolysis has become an integral component of aesthetic medicine, the international association of physicians performing lipolysis in the so-called “*NETWORK-Lipolysis*” (with more than 2,000 members worldwide) has called for the development of internationally recognized treatment standards and protocols to improve the practice of using injection lipolysis.⁽⁸⁸⁾ However, neither PC nor DC is approved drug in the United States of America to eliminate fat. In fact, there are currently no FDA-approved drugs for injection for fat elimination because FDA cannot assure the safety and efficacy of these types of drugs.⁽⁹⁰⁾

To date, the main reported side effects of injection of PC formulations are relatively minor, and include swelling, bruising, and sensitivity to touch under the skin in areas with the lipodissolution treatments.⁽⁸⁹⁾ Additionally, Kopera and co-workers⁽¹¹³⁾ as well as others reported fascinating and promising data about the treatment of lipomas by intralesional application of PC/DC. However, several authors raised many observations regarding the safety of such treatments. For instance, Rotunda and co-workers (2005)⁽¹¹⁴⁾ showed that that DC, the detergent component of injectable PC formulation, causes nonspecific lysis of cell membranes. Thus, such formula can affect muscle tissue or tendons near the lipoma, leading to possible necrosis of these vital structures. Moreover, human fat tissue, exposed to PC/DC combinations reveals cell necrosis.⁽¹¹⁵⁾ Also, injection of DC causes focal necrosis and inflammation in human lipomas (Figure 8). These effects can be attributed to DC rather than PC, where the later plays a protective role in the preservation of cellular viability and cell membrane integrity.⁽¹¹⁶⁾ But despite this effect there are no reports suggesting long-term sequelae like focal contracture, hardening and skin dimpling or irregularity or the effect of the formula on the nearby nerves.

A



B

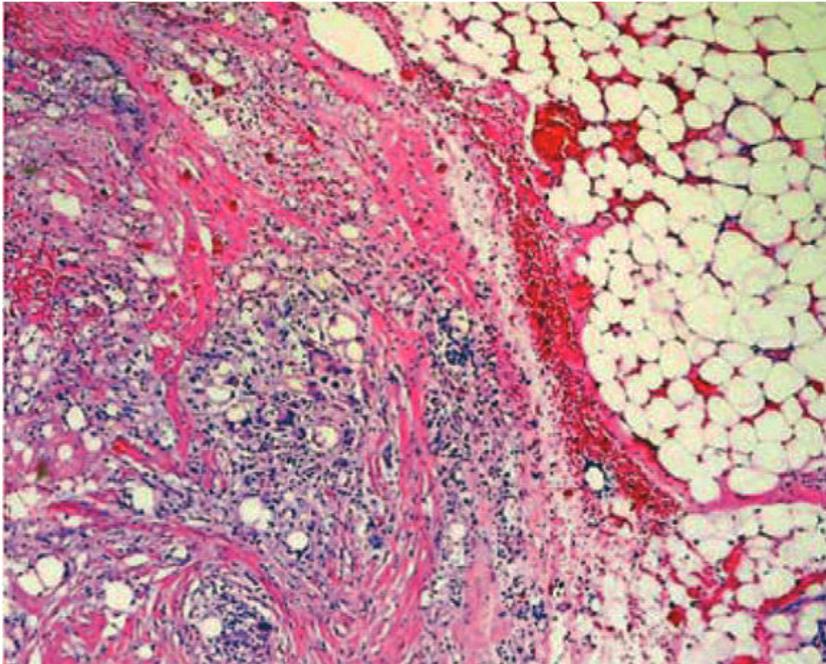


Figure 8: (A) Excised lipoma 2 days after injection with sodium deoxycholate revealing a grossly well-demarcated area of necrosis. (B) Microscopic findings demonstrating acute inflammation and necrosis (hematoxylin and eosin stain).⁽⁸⁹⁾

1.4. Aim of the work

The effort done in this study is to investigate the effect of local PC/DC (Lipostabil N ®) injections, which is commonly used in injectable lipolysis, on neurological structures. This is accomplished by observing the possible histopathological changes that may result from injection of PC/DC in rats near main nerves. The importance of this work is drawn from two important issues: First, the possibility that off-label use of local PC/DC injection to remove lipomas in practice might affect the nearby nerves integrity and, second, to assess the safety of utilizing this combination as an alternative for surgery in treating intra-spinal and neural lipomas.