Lipomas: genetic basis of common skin lesions and their occurrence in rare diseases

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Abstract

Lipomas are usually sporadic, asymptomatic lesions, and their clinical and histologic presentation does not pose diagnostic difficulties. In ambiguous cases, however, knowledge of genetics is necessary. HMGA2 expression in adipose cells enables the differentiation of normal adipose tissue from lipoma and liposarcoma. Moreover, lipomas can be associated with genetic diseases, such as multiple endocrine neoplasia type 1, neurofibromatosis type 1, Wilson's disease, or mitochondrial diseases. Lipomas can run in families (familial multiple lipomatosis) or be a part of genetic syndromes such as PTEN hamartoma tumor syndrome, Proteus syndrome, and Pai syndrome. This study aims to present the genetic basis of lipomas and diseases in which these lesions occur in the clinical picture.

Key words: lipoma, HMGA2, Dercum's disease, orphan diseases.

Introduction

Lipomas are the most common soft tissue tumours and occur in about 1% of the population. Physicians evaluate subcutaneous lipomas by palpation, imaging studies, and pathomorphological examination. An additional tool that is gaining in value is genetic testing, which can help in making the correct diagnosis in complicated cases or in differentiating ambiguous lesions. In this review, we focus primarily on the genetic background of lipomas and on the diseases and genetic syndromes in which they coexist. Our aim is to sensitize readers to the fact that even a common lesion may prove to be part of a more complex, rare problem.

Classification and pathomorphology

Lipomas belong to benign lipomatous neoplasms and are coded 2E80.0 according to the International Classification of Diseases 11th Revision effective of 1 January 2022. Within this group, lipomas were divided based on their location: subcutaneous (Figure 1 A), subfascial, deep internal or visceral, other specified sites, and unspecified sites. Lipomas are composed of mature white adipose tissue. They are well separated from their surroundings and are yellow to orange in colour. They have rich vascularization, but the vessels are often compressed by bloated adipocytes [1].

Signs and symptoms

Most lipomas enlarge slowly, and their presence does not cause any symptoms. The complications caused by lipomas are due to the mass effect and their pressure on surrounding structures. For instance, intracranial lipomas may cause diplopia, hydrocephalus, seizures, hearing impairment, and vertigo [2]. A lipoma compressing the superior vena cava can lead to oedema of the head, neck, and upper limb, as well as pain and numbness [3]. Additionally, chest lipomas can be responsible for shortness of breath, coughing, haemoptysis, and even angina and heart failure [4, 5]. In other reported cases, gastric lipomas have caused pain, nausea, vomiting, and gastrointestinal bleeding [6].

Diagnosis and treatment

The physician evaluates subcutaneous lipomas by palpation; lesions are usually non-painful, round, and mobile, with a characteristic soft, doughy feel [7]. For
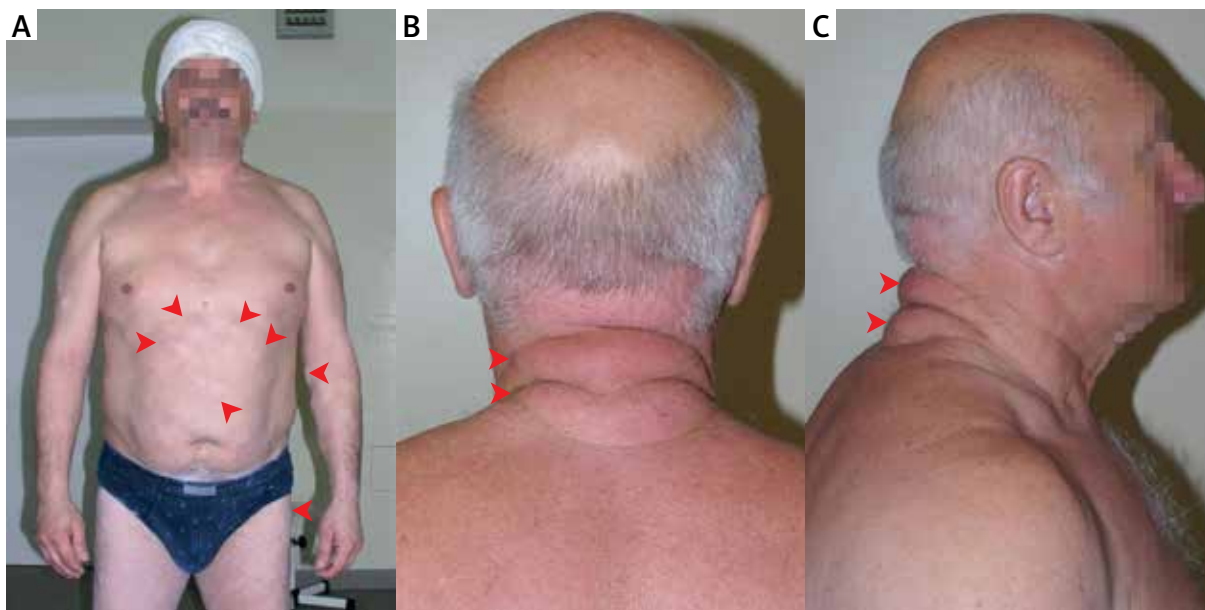
Figure 1. A – A 38-year-old man suffering from psoriasis with numerous lipomas on his abdomen and extremities. B, C – Scleromyxoedema resembling lipomas in a 64-year-old man with type 2 diabetes. Arrows indicate lesions

deep-seated lipomas, computed tomography (CT) and magnetic resonance imaging (MRI) are the best methods for visualization [2]. Sometimes other imaging studies such as radiography [8], ultrasonography [9] or much less commonly FDG-PET scan [10] and echocardiography [5] lead to the diagnosis. The pathomorphological examination uses material obtained from a fine-needle biopsy [7, 11] or a tumour resected during surgery [12]. The differential diagnosis should consider (Figures 1 B, C): liposarcoma, metastatic disease, hematoma, epidermoid cyst, nodular fasciitis, nodular subcutaneous fat necrosis, erythema nodosum, vasculitic nodules, rheumatic nodules, sarcoidosis, infections, and Weber-Christian panniculitis.

Treatment of lipomas consists in removing the lesion. Since most lipomas do not give any symptoms and the reason for treatment is aesthetic, methods that minimize the size of scars after surgery play an important role. Subcutaneous lipomas are surgically excised through an incision made in the skin overlying the mass [7]. To improve cosmetic results, surgeons use a narrow hole extrusion technique (NHET), which continues to be refined by subsequent researchers [13, 14]. Another technique used for surgical treatment is liposuction, which seems to be a good option, especially for large lipomas that would require a very long incision for classic lesion removal [15]. However, for smaller lipomas, laser lipolysis may be better [16, 17]. If the patient would like to avoid surgical treatment, injections of sodium deoxycholate [18] or corticosteroids [19] can reduce the size of lipomas. For deep-seated lipomas, the type of surgery depends on the location of the lesion and the symptoms it causes.

Genetics of sporadic lipomas

50–80% of lipomas have cells with an abnormal karyotype [20–22]. The following structural rearrangements of chromosomes, which may occur singly or in combination, have been associated with lipoma occurrence [23]: 12q13-15 region, 6p21-23 region, 13q portion loss, other loci anomalies or normal karyotype.

We most frequently observe the rearrangement of chromosome 12 in bands q13-15 [21, 22], which involve the high mobility group (HMG) protein gene located at 12q15 – *HMGA2*. This gene participates in the organization of the transcription complex and the regulation of transcription [24]. The translocation produces chimeric mRNA, in lipomas, this is usually HMGA2/LPP (lipoma preferred partner) [25]. The 12q13-15 aberration also occurs in other solid tumours, i.e. chondroid hamartomas [26], salivary gland adenomas, uterine leiomyomas, and endometrial polyps [27, 28]. Karyotypic alterations in chromosome 6 most often occur in bands p21-23 involving *HMGA1* [27]. The protein product of this gene belongs to the same family as HMGA2 and is also responsible for regulating chromatin structure [24]. Both of these genes are abundantly transcribed in embryonic and undifferentiated cells, whereas in normal mature cells, HMGA2 should not be present at all [29, 30] and HMGA1 only in small amounts [31].

Cytogenetics as a diagnostic tool

HMGA2 expression in adipose cells allows normal adipose tissue (in which HMGA2 is absent) to be distinguished from lipoma and liposarcoma (HMGA2 pres-

ent) [32]. For differentiating benign from malignant lesions, when a certain diagnosis cannot be made based on clinical and histological data, assessment of *Murine double minute 2* (*MDM2*) gene overexpression/amplification is commonly used [33–35]. Therefore, HMGA2 staining helps pathologists make the correct diagnosis and thus select the appropriate treatment for the patient [36].

Cytogenetic changes and the clinical picture

Sreekantaiah *et al.* [21] analysed the cytogenetic profiles of 109 lipomas and found several associations between cytogenetic patterns and clinical parameters. Abnormal karyotypes were seen more often in older patients, in large and deep-seated lipomas, and tumours of the head, neck, and shoulders. By contrast, the results obtained by the CHAMP Study Group showed an association only with age [22]. As a potential reason for these differences, the authors suggested a different percentage of lipomas in each location compared to Sreekantaiah's study, but they still concluded that cytogenetic changes in lipomas correlate poorly with clinical data.

Genetic diseases with lipomas

Lipomas are most often sporadic, but they can also accompany diseases caused by a germinal mutation.

Lipomas in autosomal dominant disorder

Familial multiple lipomatosis (FML) is a condition in which patients develop multiple lipomas. Most often lipomas appear in the third decade of life and their number increases until the fifth decade; numerous lesions develop gradually on the extremities and trunk [37–39]. A clinical diagnosis is made based on an evaluation of the family pedigree and the presenting symptoms of the disease in its members [37, 40]. The gene responsible for the disease has not been identified, but analysis of the pedigrees of affected families indicates autosomal dominant inheritance [40]. Unlike patients with Dercum's disease, patients with FML do not experience pain associated with lipomas, and the most common reason for treatment is aesthetic. Treatment consists of surgical excision of the lesion using techniques that minimize scarring, liposuction, and lipolysis with phosphatidylcholine [41–43]. The differential diagnosis for FML should include other diseases in which multiple lipomas appear in the clinical picture (e.g., multiple endocrine neoplasia type 1, neurofibromatosis type 1, Dercum's disease) and multiple symmetrical lipomatosis (Madelung's disease). In Madelung's disease fat tissue accumulates symmetrically on the neck, back, and upper trunk, resulting in the characteristic "horse collar" rounded appearance. It primarily affects middle-aged men who consume alcohol [44].

Another disease with autosomal dominant inheritance accompanied by lipomas is multiple endocrine neoplasia type 1 (MEN 1) – a genetic disease predisposing to parathyroid, pancreatic, and pituitary tumours. We can observe both multiple and solitary lipomas as one of the skin lesions found in these patients [45, 46]. Scientists proposed including skin lesions in the diagnostic criteria, which could facilitate the diagnosis in some complicated cases (e.g., the presence of endocrinopathies not associated with the syndrome, negative family history, poorly expressed hyperparathyroidism, unavailability of genetic tests) [45, 47]. Although lipomas are much more common in MEN 1 patients than in the general population and show high specificity, due to their low sensitivity, they cannot be one of the diagnostic criteria [45], unlike angiofibromas and collagenomas. The presence of lipomas, both subcutaneous and visceral, is found in 17% to 34% of patients [45–47]. Dreijerink *et al.* discussed the molecular basis of lipomas development in patients with MEN 1. They found that menin, absent in MEN1 patients, is an important factor in PPARγ (peroxisome proliferator-activated receptor)-mediated adipogenesis and that loss of PPARγ function contributes to lipoma development [48].

Lipomas also occur more frequently in neurofibromatosis type 1 (NF1) patients than in the general population as one of many skin lesions. In Miraglia's study involving the evaluation of cutaneous manifestations of NF1 in 1102 patients, lipomas were the fourth most common skin lesion (6.2%) [49]. Typically, lipomas appear singly, but multiple cases have also been observed [49, 50].

Given that cutaneous lipomas are rare in children, their presence should prompt a complete physical examination to look for other disease manifestations of various genetic syndromes (Table 1). One of them is Bannayan-Riley-Ruvalcaba syndrome, which belongs to a group of diseases called the PTEN hamartoma tumor syndrome (PHTS) group. This autosomal dominant disease is caused by a rare developmental defect during embryogenesis which leads to macrocephaly, neurological abnormalities, hamartomatous intestinal polyposis, genital lentiginosis, lipomas, and other cutaneous lesions [51, 52]. Martin *et al.* highlight the diagnostic problems and suggest including the presence of lipomas among the main diagnostic criteria in children [52]. In turn, early diagnosis is important because of the increased rate of malignancy in patients [53].

Lipomas in autosomal recessive disorder

This group includes Wilson's disease. Schaefer *et al.* detected subcutaneous lipomas in 21 of the 80 patients examined, with 16 cases involving multiple subcutaneous lipomas. The higher prevalence of lipomas did not associate with the severity of the disease, its presentation, or anti-copper therapy. They suggested that subcutaneous lipomas may be considered a clinical sign that could facilitate the diagnosis of this disease in some cases [54].

Table 1. Rare genetic syndromes with lipomas in clinical presentation

Disease name	Inheritance	Age of onset	Clinical signs and symptoms
Bannayan-Riley-Ruvalcaba syndrome	Autosomal dominant	Neonatal	Macrocephaly, hemangiomas, intestinal polyps, multiple subcutaneous lipomas
Nasopalpebral lipoma-coloboma syndrome	Autosomal dominant	Neonatal	Facial malformation: bilateral upper eyelid and nasopalpebral lipomas, colobomas of upper and lower eyelids, telecanthus, maxillary hypoplasia
Pai syndrome	Unknown	Neonatal	Hypertelorism with downward slanting palpebral fissures, midline cleft lip with midline nasal and facial polyps, lipomas on the forehead
Currarino syndrome	Autosomal dominant or not applicable	All ages	Anorectal malformations, presacral mass, sacral anomalies, spinal lipoma of the filum terminale
Proteus syndrome	Not applicable	Infancy	Hemihypertrophy, macrodactyly, vascular malformations, linear epidermal nevi, adipose dysregulation

Mitochondrial diseases

Lipomas also occur in certain mitochondrial diseases with specific mutations. Lipomas are reported in patients with mitochondrial diabetes associated with a tRNALeu(UUR) [55] and 3243 tRNALeu(UUR) mutation [56]. Then Larsson *et al.* described the association between the A83446 mutation of mitochondrial DNA, MERRF syndrome and multiple symmetric lipomas [57]. Furthermore, Finsterer *et al.*, after summarising studies by other authors, concluded that lipomas, especially cervical, are an important clinical feature found in MERRF cases [58].

Disorders of ambiguous aetiology

A disease of unclear pathophysiology that presents both sporadically and familial is Dercum's disease (adiposis dolorosa). On the one hand, researchers suspect that an inflammatory process underlies the disease, but the findings do not provide a clear answer. Hansson *et al.* compared the inflammatory response in fat biopsies from Dercum's disease patients with obese pain-free control patients and found no significant difference [59]. However, based on their research which compared blood samples, Lemaitre *et al.* suggested low levels of NK lymphocytes as the primary mechanism of disease development, leading to basophil activation and subsequent subclinical inflammation and pain [60]. On the other hand, the literature describes cases of familial occurrence of this disease, which indicates an autosomal dominant inheritance with different expressions [61, 62].

The characteristic of Dercum's disease is chronic pain (>3 months) in the adipose tissue and generalized overweight or obesity. After excluding all other causes of the patient's complaints, these features form the basis for the diagnosis [63]. Although the relationship between Dercum's disease, chronic pain, depression, and obesity is complex, patients with adiposis dolorosa are significantly more likely to suffer from depression than obese

healthy controls [64, 65]. Patients also complain of sleep disturbances, impaired memory, difficulty concentrating, anxiety, rapid heartbeat, shortness of breath, diabetes, bloating, constipation, fatigue, weakness, and joint aches [63–65].

This rare disease affects women more often than men and appears between the ages of 35 and 50 [60, 64, 66]. Cases of Dercum's disease fall into one of four groups [63]: patients present with a generalised diffuse form (widespread painful adipose tissue without lipoma) [67], a generalised nodular form (general pain in adipose tissue and increased sensitivity surrounding lipomas), a localised nodular form (pain in and around multiple lipomas), and a juxta-articular form (painful adipose tissue near large joints) [68]. In the nodular form of the disease, multiple subcutaneous lipomas appear on the back, thighs, and arms [60, 66], which usually present histologically as ordinary lipomas [59, 61], but sometimes individual lesions can demonstrate angiolipoma or spindle cell lipoma [66].

There are no clear treatment guidelines, but the key point is pain relief. Treatment includes surgical procedures such as excision of lipomas or liposuction, as well as various pharmacological agents [63]. Excision of the lesions is often ineffective and results in only a partial improvement due to the appearance of new lipomas [69], while the long-term efficacy of liposuction is difficult to assess because of the simultaneous use of different forms of treatment by patients [67]. Pharmacological treatment includes non-steroidal anti-inflammatory drugs (which are not very effective), narcotic drugs, lidocaine (both systemic and in the form of a patch), interferon alpha-2b, corticosteroids, and calcium channel modulators, such as pregabalin and oxcarbazepine [63].

Conclusions

Genetic knowledge and testing are useful in clinical practice for lipomas. They help differentiate between nor-

mal fat tissue, lipoma, and liposarcoma. Moreover, the presence of lipomas can lead to the correct diagnosis of various diseases and, therefore, the application of appropriate treatment.

Conflict of interest

The authors declare no conflict of interest.

References

1. Murphey MD, Carroll JF, Flemming DJ, et al. From the archives of the AFIP. RadioGraphics 2004; 24: 1433-66.
2. Romano N, Castaldi A. Imaging of intracranial fat: from normal findings to pathology. Radiol Med 2021; 126: 971-8.
3. Sundaram N, Kulkarni R, Sultan I, et al. Surgical resection of a symptomatic superior vena cava lipoma: a case report and literature review. Ann Vasc Surg 2020; 71: 535.e11-e15.
4. Akar E, Haberal M, Dikis O. Diagnostic and therapeutic treatment methods for intrathoracic extrapulmonary lipomas. Niger J Clin Pract 2020; 23: 626-30.
5. D'Souza J, Shah R, Abbass A, et al. Invasive cardiac lipoma: a case report and review of literature. BMC Cardiovasc Disord 2017; 17: 28.
6. Cappell MS, Stevens CE, Amin M. Systematic review of giant gastric lipomas reported since 1980 and report of two new cases in a review of 117110 esophagogastroduodenoscopies. World J Gastroenterol 2017; 23: 5619-33.
7. El-Monem MHA, Gaafar AH, Magdy EA. Lipomas of the head and neck: presentation variability and diagnostic work-up. J Laryngol Otol 2006; 120: 47-55.
8. Eren F, Candan T, Eren B, et al. Endobronchial lipoma. J Pak Med Assoc 2013; 63: 784-5.
9. Wagner JM, Rebik K, Spicer PJ. Ultrasound of soft tissue masses and fluid collections. Radiol Clin North Am 2019; 57: 657-69.
10. Sakurai H, Kaji M, Yamazaki K, et al. Intrathoracic lipomas: their clinicopathological behaviors are not as straightforward as expected. Ann Thorac Surg 2008; 86: 261-5.
11. Arslan IB, Uluyol S, Genc S, et al. Diagnostic dilemma of parotid lipomas: imaging versus fine needle aspiration cytology. Bosn J Basic Med Sci 2014; 14: 250-3.
12. Aita TG, Bonardi JP, Stabile GAV, et al. Lipoma on the lower lip. J Craniofac Surg 2017; 28: e750-1.
13. Gupta S, Pandhi R, Kumar B. Pot-lid' technique for aesthetic removal of small lipoma on the face. Int J Dermatol 2001; 40: 420-4.
14. Chandawarkar RY, Rodriguez P, Roussalis J, Tantri MD. Minimal-scar segmental extraction of lipomas: study of 122 consecutive procedures. Dermatol Surg 2005; 31: 59-64.
15. Choi CW, Kim BJ, Moon SE, et al. Treatment of lipomas assisted with tumescent liposuction. J Eur Acad Dermatol Venereol 2007; 21: 243-6.
16. Goldman A, Wollina U. Lipoma treatment with a subdermal Nd:YAG laser technique. Int J Dermatol 2009; 48: 1228-32.
17. Stebbins GW, Hanke CW, Petersen J. Novel method of minimally invasive removal of large lipoma after laser lipolysis with 980 nm diode laser. Dermatol Ther 2011; 24: 125-30.
18. Rotunda AM, Ablon G, Kolodney MS. Lipomas treated with subcutaneous deoxycholate injections. J Am Acad Dermatol 2005; 53: 973-8.
19. Redman LM, Moro C, Dobak J, et al. Association of β-2 adrenergic agonist and corticosteroid injection in the treatment of lipomas. Diabetes Obes Metab 2011; 13: 517-22.
20. Fletcher CDM, Akerman M, Dal Cin P, et al. Correlation between clinicopathological features and karyotype in lipomatous tumors. A report of 178 cases from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. Am J Pathol 1996; 148: 623-30.
21. Sreekantaiah C, Leong SP, Karakousis CP, et al. Cytogenetic profile of 109 lipomas. Cancer Res 1991; 51: 422-33.
22. Willén H, Åkerman M, Dal Cin P, et al. Comparison of chromosomal patterns with clinical features in 165 lipomas: a report of the CHAMP study group. Cancer Genet Cytogenet 1998; 102: 46-9.
23. Chrisinger JSA. Update on lipomatous tumors with emphasis on emerging entities, unusual anatomic sites, and variant histologic patterns. Surg Pathol Clin 2019; 12: 21-33.
24. Tallini G, Dal Cin P. HMGI(Y) and HMGI-C dysregulation: a common occurrence in human tumors. Adv Anat Pathol 1999; 6: 237-46.
25. Petit MMR, Mols R, Schoenmakers EFPM, et al. LPP, the preferred fusion partner gene of HMGIC in lipomas, is a novel member of the LIM protein gene family. Genomics 1996; 36: 118-29.
26. Fletcher JA, Longtine J, Wallace K, et al. Cytogenetic and histologic findings in 17 pulmonary chondroid hamartomas: evidence for a pathogenetic relationship with lipomas and leiomyomas. Genes Chromosomes Cancer 1995; 12: 220-3.
27. Tallini G, Vanni R, Manfioletti G, et al. HMGI-C and HMGI(Y) immunoreactivity correlates with cytogenetic abnormalities in lipomas, pulmonary chondroid hamartomas, endometrial polyps, and uterine leiomyomas and is compatible with rearrangement of the HMGI-C and HMGI(Y) genes. Lab Invest 2000; 80: 359-69.
28. Van de Ven WJM, Schoenmakers EFPM, Wanschura S, et al. Molecular characterization of MAR, a multiple aberration region on human chromosome segment 12q13-q15 implicated in various solid tumors. Genes Chromosomes Cancer 1995; 12: 296-303.
29. Manfioletti G, Giancotti V, Bandiera A, et al. cDNA cloning of the HMGI-C phosphoprotein, a nuclear protein associated with neoplastic and undifferentiated phenotypes. Nucleic Acids Res 1991; 19: 6793-7.
30. Rogalla P, Drechsler K, Frey G, et al. HMGI-C expression patterns in human tissues. Implications for the genesis of frequent mesenchymal tumors. Am J Pathol 1996; 149: 775-9.
31. Chiappetta G, Avantaggiato V, Visconti R, et al. High level expression of the HMGI (Y) gene during embryonic development. Oncogene 1996; 13: 2439-46.
32. Dreux N, Marty M, Chibon F, et al. Value and limitation of immunohistochemical expression of HMGA2 in mesenchymal tumors: about a series of 1052 cases. Mod Pathol 2010; 23: 1657-66.
33. Putri RI, Siregar NC, Siregar B. Overexpression and amplification of Murine double minute 2 as a diagnostic tool in large lipomatous tumor and its correlation with Ki67 proliferation index: an institutional experience. Indian J Pathol Microbiol 2014; 57: 558-63.
34. Sirvent N, Coindre JM, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. Am J Surg Pathol 2007; 31: 1476-89.
35. Wong DD, Low IC, Peverall J, et al. MDM2/CDK4 gene amplification in large/deep-seated "lipomas": incidence, predictors and clinical significance. Pathology 2016; 48: 203-9.
36. Piton N, Angot É, Marguet F, et al. HMGA2 immunostaining is a straightforward technique which helps to distinguish

pulmonary fat-forming lesions from normal adipose tissue in small biopsies: a retrospective observational study about a series of 13 lung biopsies. Diagn Pathol 2017; 12: 21.

37. Gologorsky D, Gologorsky Y, Yarygina AS, et al. Familial multiple lipomatosis: report of a new family. Cutis 2007; 79: 227-32.

38. Kurzweg FT, Spencer R. Familial multiple lipomatosis. Am J Surg 1951; 82: 762-5.

39. Veger HTC, Ravensbergen NJC, Ottenhof A, et al. Familial multiple lipomatosis: a case report. Acta Chir Belg 2010; 110: 98-100.

40. Lee CH, Spence RAJ, Upadhyaya M, et al. Familial multiple lipomatosis with clear autosomal dominant inheritance and onset in early adolescence. BMJ Case Rep 2011; 2011: bcr1020103395.

41. Bechara FG, Sand M, Sand D, et al. Lipolysis of lipomas in patients with familial multiple lipomatosis: an ultrasonography-controlled trial. J Cutan Med Surg 2006; 10: 155-9.

42. Hallock GG. Endoscope-assisted suction extraction of lipomas. Ann Plast Surg 1995; 34: 32-4.

43. Ronan SJ, Broderick T. Minimally invasive approach to familial multiple lipomatosis. Plast Reconstr Surg 2000; 106: 878-80.

44. Liu Q, Lyu H, Xu B, Lee JH. Madelung disease epidemiology and clinical characteristics: a systemic review. Aesthetic Plast Surg 2021; 45: 977-86.

45. Asgharian B, Turner ML, Gibril F, et al. Cutaneous tumors in patients with multiple endocrine neoplasm type 1 (MEN1) and gastrinomas: prospective study of frequency and development of criteria with high sensitivity and specificity for MEN1. J Clin Endocrinol Metab 2004; 89: 5328-36.

46. Vidal A, Iglesias MJ, Fernández B, et al. Cutaneous lesions associated to multiple endocrine neoplasia syndrome type 1. J Eur Acad Dermatol Venereol 2008; 22: 835-8.

47. Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol 1997; 133: 853-7.

48. Dreijerink KMA, Varier RA, van Beekum O, et al. The multiple endocrine neoplasia type 1 (MEN1) tumor suppressor regulates peroxisome proliferator-activated receptor gamma-dependent adipocyte differentiation. Mol Cell Biol 2009; 29: 5060-9.

49. Miraglia E, Moliterni E, Iacovino C, et al. Cutaneous manifestations in neurofibromatosis type 1. Clin Ter 2020; 17: 371-7.

50. Miraglia E, Fino P, Lopez T, et al. Multiple lipomas in a patient with neurofibromatosis type 1. G Ital Dermatol Venereol 2019; 154: 734-35.

51. Lynch NE, Lynch SA, McMenamin J, et al. Bannayan-Riley-Ruvalcaba syndrome: a cause of extreme macrocephaly and neurodevelopmental delay. Arch Dis Child 2009; 94: 553-4.

52. Martin H, Bessis D, Bourrat E, et al. Cutaneous lipomas and macrocephaly as early signs of PTEN hamartoma tumor syndrome. Pediatr Dermatol 2020; 37: 839-43.

53. Gujrati M, Thomas C, Zelby A, et al. Bannayan-Zonana syndrome: a rare autosomal dominant syndrome with multiple lipomas and hemangiomas: a case report and review of literature. Surg Neurol 1998; 50: 164-8.

54. Schaefer M, Gotthardt DN, Didion C, et al. Increased prevalence of subcutaneous lipomas in patients with Wilson disease. J Clin Gastroenterol 2015; 49: 61-3.

55. Suzuki Y, Suzuki S, Hinokio Y, et al. Diabetes associated with a novel 3264 mitochondrial tRNA (Leu)(UUR) mutation. Diabetes Care 1997; 20: 1138-40.

56. Suzuki Y, Nishimaki K, Taniyama M, et al. Lipoma and opthalmoplegia in mitochondrial diabetes associated with small heteroplasmy level of 3243 tRNA(Leu(UUR)) mutation. Diabetes Res Clin Pract 2004; 63: 225-9.

57. Larsson NG, Tulinius MH, Holme E, et al. Pathogenetic aspects of the A8344G mutation of mitochondrial DNA associated with MERRF syndrome and multiple symmetric lipomas. Muscle Nerve Suppl 1995; 3: S102-6.

58. Finsterer J, Zarrouk-Mahjoub S, Shoffner JM. MERRF classification: implications for diagnosis and clinical trials. Pediatr Neurol 2018; 80: 8-23.

59. Hansson E, Svensson H, Stenram U, et al. Histology of adipose tissue inflammation in Dercum's disease, obesity and normal weight controls: a case control study. J Inflamm 2011; 8: 24.

60. Lemaitre M, Chevalier B, Jannin A, et al. Metabolic and immunological phenotype of rare lipomatoses: Dercum's disease and Roch-Leri mesosomatic lipomatosis. Orphanet J Rare Dis 2021; 16: 290.

61. Campen R, Mankin H, Louis DN, et al. Familial occurrence of adiposis dolorosa. J Am Acad Dermatol 2001; 44: 132-6.

62. Cantu JM, Ruiz-Barquin E, Jimenez M, et al. Autosomal dominant inheritance in adiposis dolorosa (Dercum's disease). Humangenetik 1973; 18: 89-91.

63. Hansson E, Svensson H, Brorson H. Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management. Orphanet J Rare Dis 2012; 7: 23.

64. Beltran K, Herbst KL. Differentiating lipedema and Dercum's disease. Int J Obes 2017; 41: 240-5.

65. Hansson E, Svensson H, Brorson H. Depression in Dercum's disease and in obesity: a case control study. BMC Psychiatry 2012; 12: 74.

66. Tins BJ, Matthews C, Haddaway M, et al. Adiposis dolorosa (Dercum's disease): MRI and ultrasound appearances. Clin Radiol 2013; 68: 1047-53.

67. Hansson E, Svensson H, Brorson H. Liposuction may reduce pain in Dercum's disease (adiposis dolorosa). Pain Med 2011; 12: 942-52.

68. Wollina U, Heinig B, Langner D, et al. Juxta-articular adiposis dolorosa (Dercum's disease type IV): report of four cases and treatment by dermolipectomy. Wien Med Wochenschr 2015; 165: 374-7.

69. Lam A, Aukerman W, Winegarden B, et al. Lurking under the surface: Dercum's disease. Cureus 2021; 13: 17649.