AOTH

Case Report

Retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastasis in soft tissue, in the context of lipomatosis: a case report

Shinji Tsukamoto[1], Kanya Honoki[1], Alberto Righi[2], Marco Gambarotti[2], Angelo Paolo Dei Tos[2,3], Costantino Errani[4], Shingo Kishi[1,5], Yasuhito Tanaka[1], Hiroki Kuniyasu[5]

[1]*Department of Orthopaedic Surgery, Nara Medical University, Kashihara, Nara, Japan.*
[2]*Department of Pathology, IRCCS Rizzoli Institute, Bologna, Italy.*
[3]*University of Padua School of Medicine, Azienda ULSS 2 Marca Trevigiana, Treviso, Italy.*
[4]*Department of Orthopaedic Oncology, IRCCS Rizzoli Institute, Bologna, Italy.*
[5]*Department of Molecular Pathology, Nara Medical University, Kashihara, Nara, Japan.*

Abstract

Lipomatosis is a diffuse overgrowth of mature adipose tissue. Point mutations in mitochondrial genes have been implicated in its pathogenesis, which increase oxidative stress. Nine cases of sarcoma associated with lipomatosis have been reported to date, of which only one was a dedifferentiated liposarcoma. We report a case of retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastases in soft tissue, in the context of lipomatosis. Expression of 4-hydroxy-2-nonenal and 8-hydroxy-2'-deoxyguanosine as markers of oxidative stress increased in sarcoma cells invading the pancreas. This case indicates the potential for the generation of dedifferentiated liposarcoma in lipomatosis via oxidative stress and underscores the necessity for follow-up of patients with lipomatosis.

Keywords

Dedifferentiated liposarcoma; multiple lipomas; lipomatosis; 4HNE; 8-OHdG

Corresponding author

Shinji Tsukamoto, MD, Department of Orthopaedic Surgery
email: shinji104@mail.goo.ne.jp

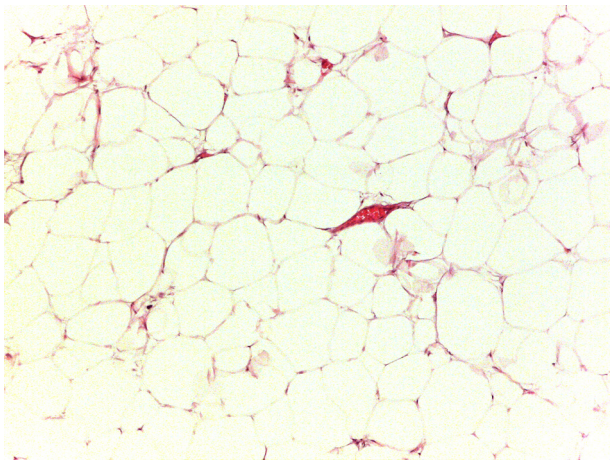

Fig. 1 *Hematoxylin and eosin staining showing lobules of mature adipocytes without any cytological atypia (a: 50x magnification; b: 200x magnification).*

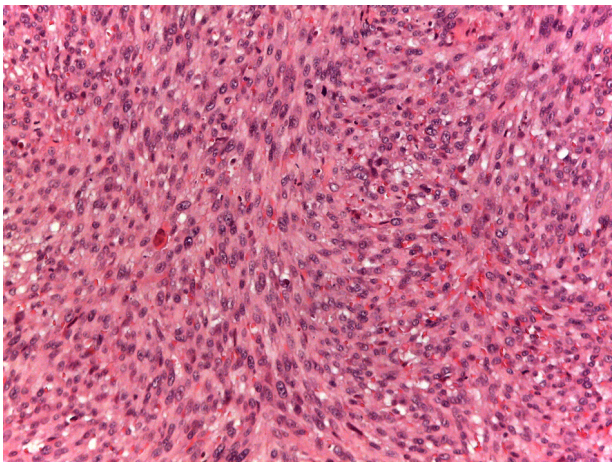

Fig. 2 *Malignant spindle cell neoplasm suspected of sarcoma was evident on hematoxylin and eosin staining (a: 50x magnification; b: 200x magnification).*

Introduction

Lipomatosis is a diffuse overgrowth of mature adipose tissue.[1] The basic mechanism underlying lipomatosis is not well-understood. In some cases, an autosomal dominant inheritance has been suggested.[2] The 8344 mutation in the transfer RNA^{Lys} gene of mitochondrial DNA has been implicated in the pathogenesis of symmetric lipomatosis.[3] Nine cases of sarcoma associated with lipomatosis have been reported to date: four atypical lipomatous tumors, three myxoid liposarcomas, one dedifferentiated liposarcoma, and one pleomorphic liposarcoma (Table 1).[4–11] We report a case of retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastases in soft tissue, in the context of lipomatosis. Moreover, we investigated the increase of oxidative stress due to mitochondrial dysfunction, performing immunohistochemistry for 4-hydroxy-2-nonenal (4HNE) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), which are representative biomarkers for oxidative stress, on an operative specimen.[12,13]

Case presentation

A 60-year-old man presented with multiple subcutaneous tumors. He had one tumor in the abdomen, nine in the right upper extremity, and 15 in the left upper extremity 10 years ago. All the tumors had been marginally resected at another hospital eight years ago. Examination of the largest abdominal tumor measuring 3 cm led to a diagnosis of lipoma without any cytological atypia (Fig. 1a, b). He noticed a rapidly growing mass in his left chest wall, where a lipoma had not existed six months before and visited the previous hospital. He had a subcutaneous tumor in his left chest wall (4 cm) and left forearm (2 cm), and these two tumors were resected marginally. Pathological diagnosis of the forearm tumor indicated a lipoma, while the tumor of the chest wall was suspected to be a sarcoma (Fig. 2a, b). He was referred to our hospital for additional treatment. His medical history revealed a diagnosis of urinary calculus at the age of 30 years, diabetes from the age of 40 years, and hyperuricemia and hyperlipidemia from 50 years of age. His family history revealed his mother had multiple lipomas and his father had urinary bladder cancer. Physical examination revealed a 3-cm operation scar with a subcutaneous tumor measuring 3 cm. The tumor was elastic, soft, non-adhesive, and not tender. Laboratory investigations showed increased Cr (1.18 mg/dl) and HbA1c (7.1%) levels. Tumor markers (CEA, CA19-9, CA125, CYFRA, NSE, and DUPAN-2) were all negative upon testing. On computed tomography (CT) images, after intravenous injection of contrast medium, contrast uptake by the 4-cm subcutaneous tumor in the left chest wall was observed. There was no lipomatous compo-

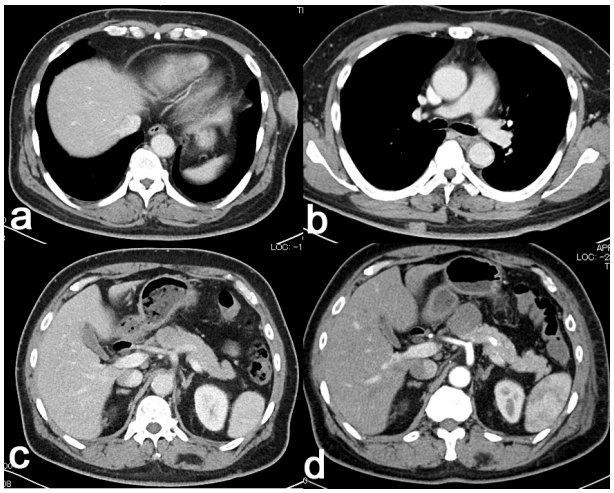

Fig. 3 *(a) CT scans after intravenous injection of contrast medium showed a subcutaneous tumor (4 cm) in the left chest wall with uptake of contrast. There was no lipomatous component. CT scans showed (b) a subcutaneous tumor (2 cm) in the right back with uptake of contrast and (c) a lipomatous tumor (3 cm) with low attenuation in the left longissimus muscle. (d) Abdominal CT showed a well-circumscribed, poorly enhanced mass measuring about 3 cm in diameter in the body of the pancreas. There was no sign of dilatation of the distal pancreatic ducts. CT, computed tomography.*

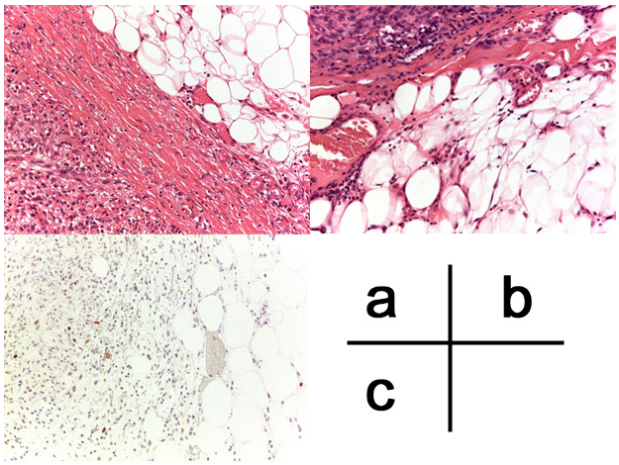

Fig. 4 *The subcutaneous tumor in the left chest wall (a: 100x magnification; b: 200x magnification) and the subcutaneous tumor in the right back (c: 200x magnification) evidenced the same morphological features consistent with dedifferentiated liposarcoma, showing MDM2 nuclear expression in low- and high-grade components (d: 200x magnification).*

nent (Fig. 3a). On CT scans, a subcutaneous tumor (2 cm) in the right back was also observed with contrast uptake (Fig. 3b). CT scans showed a 3-cm lipomatous tumor of low attenuation in the left longissimus muscle (Fig. 3c). Abdominal CT showed a well-circumscribed, poorly enhanced mass measuring about 3 cm in diameter in the body of the pancreas. There was no sign of dilatation of the distal pancreatic ducts (Fig. 3d). First, wide resection of the two tumors of the chest wall was performed. Both tumors were resected *en bloc* with the underlying fascia and a horizontal 3-cm margin. Skin defects were sutured. Histological examination of both lesions revealed spindle cell malignant, grade 3 lesions, according to the Fédération nationale des centres de lutte contre le cancer (FNCLCC) grading system for mesenchymal neoplasms (Fig. 4a-c). In particular, the morphological and immunohistochemical features (MDM2 nuclear expression [Fig. 4d] and all other markers [desmin, S100 protein, CD34, CD31, cytokeratin AE1/AE3, caldesmon, cytokeratin CAM 5.2, smooth muscle actin, factor VIII, HMB45, EMA, c-Kit, CD56, and melan A negative) are consistent with the diagnosis of dedifferentiated liposarcoma. Magnetic resonance imaging of the abdomen showed a well-circumscribed mass measuring 4 cm in diameter and applying pressure on the body of the pancreas. The mass was homogenously hypointense on T1-weighted images (Fig. 5a), but non-homogenously slightly hyperintense on T2-weighted images (Fig. 5b) and showed slight enhancement with gadolinium diethylene triaminepentaacetic acid on T1-weighted fat suppression images (Fig. 5c). The radiological differential diagnosis included a metastasis from dedifferentiated liposarcoma of the chest wall, malignant lymphoma, or hypovascular neoplasm of the endocrine pancreas. The patient underwent endoscopic ultrasonography-guided fine needle aspiration biopsy of the pancreatic lesion. Cell block examination obtained from the pancreatic lesion showed a prevalent spindle cell malignant tumor with cytological atypia resembling the high-grade component of dedifferentiated liposarcoma of the chest wall tumors (Fig. 6a, b). We therefore performed central pancreatectomy because it was impossible to separate the tu-

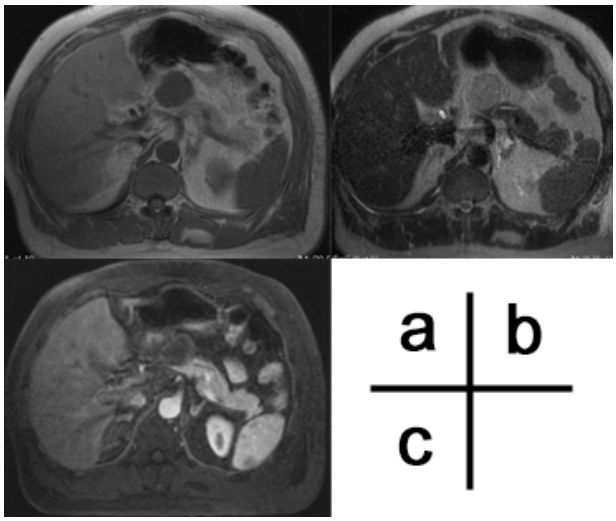

Fig. 5 *Magnetic resonance imaging of the abdomen showed a well-circumscribed mass measuring 4 cm in diameter and applying pressure on the body of the pancreas. The mass was (a) homogenously hypointense on T1-weighted images, (b) non-homogenously slightly hyperintense on T2-weighted images, and (c) showed slight enhancement with gadolinium diethylene triaminepentaacetic acid on T1-weighted fat suppression images.*

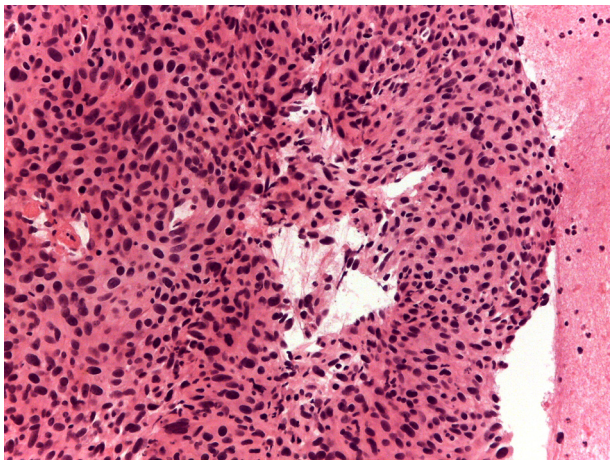

Fig. 6 *Hematoxylin and eosin staining relative to cell block obtained of the pancreatic lesion that showed a prevalent spindle cell malignant tumor with cytology consistent with the high-grade component of dedifferentiated liposarcoma (a: 100x magnification; b: 200x magnification).*

mor adhered to the body of the pancreas. Histological examination of the specimen showed localization of the high-grade component of dedifferentiated liposarcoma (Fig. 7). Together with the histological findings, the final diagnosis was retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastases in soft tissue. Postoperatively, pancreatic fistula occurred, and the patient was treated with antibacterial agents, drainage, and protease inhibitors. F-18 fluorodeoxyglucose positron emission tomography/CT showed increased fluorodeoxyglucose uptake in the right adrenal gland and in multiple bones three months after the surgery for the pancreatic lesion. Pazopanib administration for two months failed to suppress tumor growth, and the patient died one year and one month after the surgery for the pancreatic lesion. Immunohistochemistry for 4HNE and 8-OHdG was performed on formalin-fixed tissue of the left chest wall and pancreatic tumors, demonstrating near-negativity for 4HNE in fat cells, weak positivity in a few sarcoma cells of the primary pancreatic tumor, and diffuse positivity in sarcoma cells invading the pancreas (Fig. 8a-c). Regarding 8-OHdG, weak positivity in a few sarcoma cells of the primary pancreatic tumor and weak positivity in more than half of the sarcoma cells invading the pancreas was observed (Fig. 9a, b).

Discussion

We report a case of retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastases in soft tissue, in the context of lipomatosis. The patient had distant metastasis after resection of the sarcomas and died, as in the case of dedifferentiated liposarcoma of the lower leg reported by Starkloff et al. in 1951 (Table 1).[5]

Approximately 5–8% of all patients with lipomas have multiple tumors that are grossly and microscopically indistinguishable from solitary lipomas.[14] Lipomatosis (multiple lipomas) vary in number from a few to several hundred lesions, and they occur predominantly in the upper half of the body, with a predilection for the back, shoulder, and upper arms, as observed in our case.[14] Associated hypercholesterolemia has been noted repeatedly and it was also present in our case.[15]

Most cases of lipomatosis seem to be inherited in an autosomal dominant manner.[16] In our case,

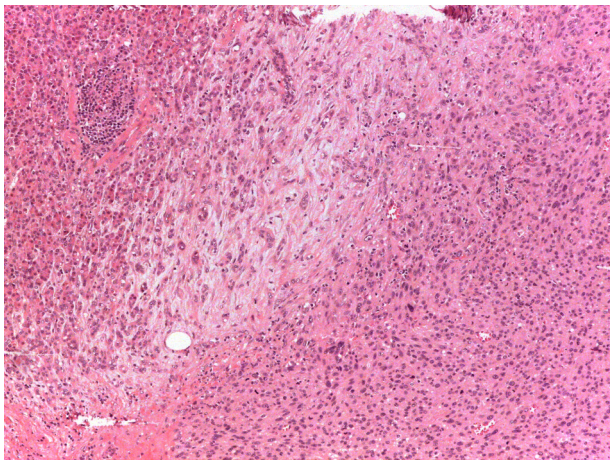

Fig. 7 *On hematoxylin and eosin staining, the localization of the high-grade component of dedifferentiated liposarcoma (on the right of the figure) was observed in the pancreatic tissue (on the left of the figure, 100x magnification)*

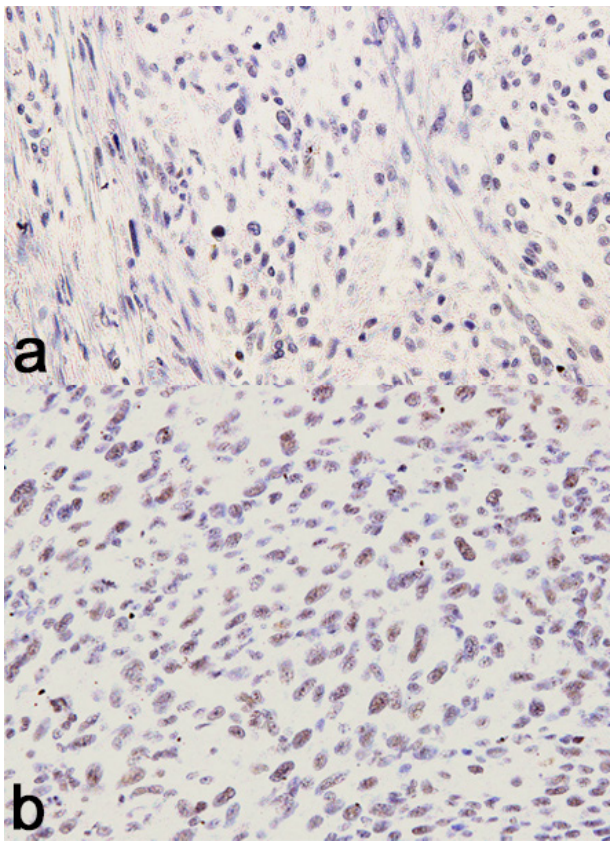

Fig. 9 *Immunohistochemistry of 8-OHdG (clone N45.1, dilution 1:200; Nikken Seil) demonstrating weak positivity in a few sarcoma cells of the primary pancreatic tumor (a: 200x magnification) and weak positivity in more than half of the sarcoma cells invading the pancreas (b: 200x magnification).*

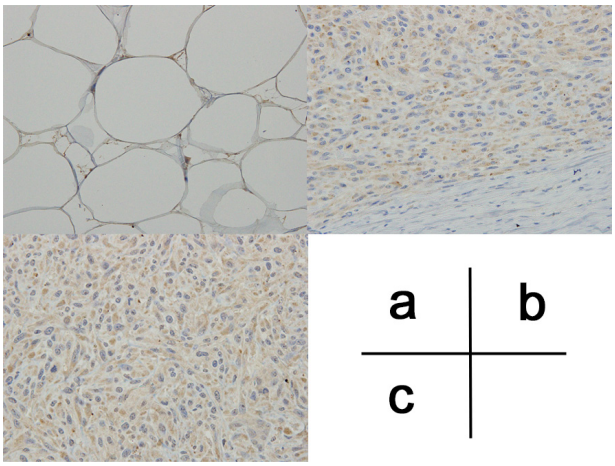

Fig. 8 *Immunohistochemistry of 4HNE (clone HNEJ-2, dilution 1:100; Nikken Seil) demonstrating near-negativity in fat cells (a: 200x magnification), weak positivity in a few sarcoma cells of the primary pancreatic tumor (b: 200x magnification), and diffuse positivity in sarcoma cells invading the pancreas (c: 200x of magnification).*

the patient's mother had lipomatosis as well. Familial multiple symmetric lipomatosis have the 8344 mutation in the transfer RNA^{Lys} gene of mitochondrial DNA.[3] The cells harboring the mutation contain mitochondria with an abnormal ultrastructure, produce increased levels of reactive oxygen species, and express upregulated antioxidant genes.[17] Mitochondria are intracellular organelles in eukaryotic cells that participate in bioenergetic metabolism and cellular homeostasis, including the generation of adenosine triphosphate (ATP) through electron transport and oxidative phosphorylation, in conjunction with the oxidation of metabolites by the tricarboxylic acid cycle and catabolism of fatty acids by β-oxidation. Mitochondrial dysfunction caused by mitochondrial DNA mutations increases the production of reactive oxygen species, and the initiation and execution of apoptosis.[18,19] Mitochondria contain multiple copies of mitochondrial DNA.[20] Human mitochondrial DNA is a 16.6-kb, double-stranded, circular DNA molecule that encodes 13 respiratory enzyme complex polypeptides, 22 transfer RNAs, and 2 ribosomal RNAs required for mitochondrial protein synthesis.[21] Because mitochondrial DNA is essential for the maintenance of functionally com-

Table 1 Literature review of sarcomas associated with lipomatosis

Sr No.	Author (Year)	Age (years) / Sex	Site	Histology	Treatment	Outcome
1	Farbman (1950)[4]	52/M	Retroperitoneum	Myxoid liposarcoma	Resection + high-voltage roentgen ray therapy	DOOD (4 mo.)
2	Starkloff et al. (1951)[5]	56/M	Femoral region	Atypical lipomatous tumor	Resection	CDF (21 mo.)
		62/F	Lower leg	Dedifferentiated liposarcoma	Amputation	DOD (15 mo.)
3	Tizian et al. (1983)[6]	57/F	Neck	Myxoid liposarcoma	Resection + chemotherapy	NA
4	Barkhof et al. (1991)[7]	60/M	Retroperitoneum	Myxoid liposarcoma	Resection	CDF (12 mo.)
			Mesenterium	Atypical lipomatous tumor	Resection	
5	Amato et al. (1998)[8]	75/F	Sigmoid mesocolon	Atypical lipomatous tumor	Resection	CDF (24 mo.)
6	Eisenstat et al. (2000)[9]	56/F	Mediastinum	Pleomorphic liposarcoma	Partial resection	NA
7	Matsumoto et al. (2000)[10]	71/M	Scapular region	Atypical lipomatous tumor	Wide resection	CDF (10 mo.)
8	Borriello et al. (2012)[11]	59/F	Axilla	Atypical lipomatous tumor	Resection + chemotherapy	NA

Sr, series; DOOD, death of other disease; CDF, continuous disease-free; DOD, death of disease; NA, not available; mo., months

petent organelles, the accumulation of mitochondrial DNA mutations or decreased mitochondrial DNA copy number is expected to affect energy production and enhance reactive oxygen species generation and cell survival, and these processes may be involved in aging, mitochondrial diseases, or cancer.[22–25] In our case, oxidative stress increased in sarcoma cells invading the pancreas, which might have contributed to the generation and progression of dedifferentiated liposarcoma. Indeed, mitochondrial DNA mutations are associated with higher grades of glioma.[26]

Seventeen cases of cancer associated with multiple symmetric lipomatosis have been reported to date: one adenocarcinoma of the urinary bladder, one Hürthle cell carcinoma of the thyroid, two squamous cell carcinomas of the head and neck, one breast cancer, one appendiceal adenocarcinoma, one breast cancer, and ten papillary carcinomas of the thyroid.[11,27–31] Hartley et al. reported that the presence of multiple lipomas might act as a marker for genetic susceptibility to malignant disease in certain families.[32]

The definitive evidence that lipomatosis is responsible for tumorigenesis is lacking. However, this case indicates the potential for the generation of dedifferentiated liposarcoma in lipomatosis via oxidative stress and underscores the necessity for follow-up of patients with lipomatosis. It is important to recruit lipomatosis patients with long-term follow-up and determine the incidence of this tumor.

Sources of funding

None

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were asper the ethical standards of the institutional and/or national research committee and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The independent ethics committee of the authors' institution approved this study.

Consent to participate

The need for informed consent was waived.

Consent for publication

The need for informed consent was waived.

References

1. Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone. Lyon: IARC, 2013.
2. Klopstock T, Naumann M, Seibel P, Shalke B, Reiners K, Reichmann H. Mitochondrial DNA mutations in multiple symmetric lipomatosis. Mol Cell Biochem. 1997;174(1-2):271-275.
3. Gámez J, Playán A, Andreu AL, et al. Familial multiple symmetric lipomatosis associated with the A8344G mutation of mitochondrial DNA. Neurology. 1998;51(1):258-260.
4. Farbman AA. Retroperitoneal fatty tumors; report of a case and collective review of the literature from 1937 to 1947. Arch Surg Chic Ill 1920. 1950;60(2):343-362, illust.
5. Starkloff GB, Saxton JA, Johnson RE. Liposarcoma of an extremity associated with multiple subcutaneous lipomas; report of two cases treated by amputation. Ann Surg. 1951;133(2):261-266.
6. Tizian C, Berger A, Vykoupil KF. Malignant degeneration in Madelung's disease (benign lipomatosis of the neck): case report. Br J Plast Surg. 1983;36(2):187-189.
7. Barkhof F, Melkert P, Meyer S, Blomjous CE. Derangement of adipose tissue: a case report of multicentric retroperitoneal liposarcomas, retroperitoneal lipomatosis and multiple subcutaneous lipomas. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 1991;17(5):547-550.
8. Amato G, Martella A, Ferraraccio F, et al. Well differentiated "lipoma-like" liposarcoma of the sigmoid mesocolon and multiple lipomatosis of the rectosigmoid colon. Report of a case. Hepatogastroenterology. 1998;45(24):2151-2156.
9. Eisenstat R, Bruce D, Williams LE, Katz DS. Primary liposarcoma of the mediastinum with coexistent mediastinal lipomatosis. AJR Am J Roentgenol. 2000;174(2):572-573. doi:10.2214/ajr.174.2.1740572
10. Matsumoto K, Hukuda S, Ishizawa M, Egawa M, Okabe H. Liposarcoma associated with multiple intramuscular lipomas. A case report. Clin Orthop. 2000;(373):202-207.
11. Borriello M, Lucidi A, Carbone A, Iannone V, Ferrandina G. Malignant transformation of Madelung's disease in a patient with a coincidental diagnosis of breast cancer: a case report. Diagn Pathol. 2012;7:116. doi:10.1186/1746-1596-7-116
12. Valavanidis A, Vlachogianni T, Fiotakis C. 8-hydroxy-2' -deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev. 2009;27(2):120-139. doi:10.1080/10590500902885684
13. Allen BG, Bhatia SK, Buatti JM, et al. Ketogenic diets enhance oxidative stress and radio-chemo-therapy responses in lung cancer xenografts. Clin Cancer Res Off J Am Assoc Cancer Res. 2013;19(14):3905-3913. doi:10.1158/1078-0432.CCR-12-0287
14. Enzinger FM, Weiss SW. Soft tissue tumors. 5th ed. St. Louis: Mosby; 2007. p. 436–7.
15. Moi L, Canu C, Pirari P, Mura MN, Piludu G, Del Giacco GS. [Dercum's disease: a case report]. Ann Ital Med Interna Organo Uff Della Soc Ital Med Interna. 2005;20(3):187-191.
16. Stoll C, Alembik Y, Truttmann M. Multiple familial lipomatosis with polyneuropathy, an inherited dominant condition. Ann Genet. 1996;39(4):193-196.
17. Chou SJ, Tseng WL, Chen CT, et al. Impaired ROS Scavenging System in Human Induced Pluripotent Stem Cells Generated from Patients with MERRF Syndrome. Sci Rep. 2016;6:23661. doi:10.1038/srep23661
18. Wallace DC, Fan W, Procaccio V. Mitochondrial energetics and therapeutics. Annu Rev Pathol. 2010;5:297-348. doi:10.1146/annurev.pathol.4.110807.092314

19. Galluzzi L, Kepp O, Kroemer G. Mitochondria: master regulators of danger signalling. Nat Rev Mol Cell Biol. 2012;13(12):780-788. doi:10.1038/nrm3479
20. Hsu CC, Tseng LM, Lee HC. Role of mitochondrial dysfunction in cancer progression. Exp Biol Med Maywood NJ. 2016;241(12):1281-1295. doi:10.1177/1535370216641787
21. Anderson S, Bankier AT, Barrell BG, et al. Sequence and organization of the human mitochondrial genome. Nature. 1981;290(5806):457-465.
22. Wallace DC. Mitochondria and cancer. Nat Rev Cancer. 2012;12(10):685-698. doi:10.1038/nrc3365
23. Lee HC, Chang CM, Chi CW. Somatic mutations of mitochondrial DNA in aging and cancer progression. Ageing Res Rev. 2010;9 Suppl 1:S47-58. doi:10.1016/j.arr.2010.08.009
24. Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat Rev Genet. 2012;13(12):878-890. doi:10.1038/nrg3275
25. Wallace DC. A mitochondrial bioenergetic etiology of disease. J Clin Invest. 2013;123(4):1405-1412. doi:10.1172/JCI61398
26. Soon BH, Abdul Murad NA, Then SM, et al. Mitochondrial DNA Mutations in Grade II and III Glioma Cell Lines Are Associated with Significant Mitochondrial Dysfunction and Higher Oxidative Stress. Front Physiol. 2017;8:231. doi:10.3389/fphys.2017.00231
27. Johnston OL, Bracken RB, Ayala AG. Vesical adenocarcinoma occurring in patient with pelvic lipomatosis. Urology. 1980;15(3):280-282.
28. Rhoads DD, Dixon AE, Taylor SA. Multiple symmetrical lipomatosis in a patient with Hürthle cell carcinoma of the thyroid: a case report. The Laryngoscope. 1986;96(1):91-95.
29. Guastella C, Borsi C, Gibelli S, Della Berta LG. Madelung's lipomatosis associated with head and neck malignant neoplasia: a study of 2 cases. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2002;126(2):191-192. doi:10.1067/mhn.2002.122004
30. Vaiphei K, Gupta N, Sinha SK, Nagi B, Singh K. Association of ulcerative colitis with pulmonary sarcoidosis, subcutaneous lipomatosis and appendiceal adenocarcinoma. Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2003;22(5):193-194.
31. Nandyala HS, Madapuram S, Yadav M, Katamala SK. Diffuse lipomatosis of the thyroid gland with papillary microcarcinoma: Report of a rare entity. Indian J Pathol Microbiol. 2015;58(3):348-350. doi:10.4103/0377-4929.162890
32. Hartley AL, Birch JM, Blair V, Harris M, Kelsey AM. Multiple lipomatosis and childhood cancer. A new association? Cancer Genet Cytogenet. 1995;80(1):17-19.

Cite this paper as

Tsukamoto S, Honoki K, Righi A, Gambarotti M, Paolo Dei Tos A, Errani C, Kishi S, Tanaka Y, Kuniyasu H. Retroperitoneal primary dedifferentiated liposarcoma with pancreatic involvement and multiple metastasis in soft tissue, in the context of lipomatosis: a case report. AOTH. 2024; 75(2): 53-60.