

CASE REPORT

Differential Diagnosis of a Case of Dercum's Disease with Possible Familial Involvement and Review of Literature

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Dercum's disease (DD), also described as adiposis dolorosa, is a poorly understood and rare adipose tissue disorder involving obesity and painful adipose tissue masses. Patients may have associated bruising and constitutional symptoms such as fatigue, difficulty concentrating, and sleep disturbance. DD was initially described in 1888 by Francis Xavier Dercum, and was classified into four subtypes, including generalized diffuse, generalized nodular, localized nodular, and juxta-articular subtypes. While this disease has been described for more than 130 years, its etiology and treatment remain elusive. We describe a case of a patient with DD who presented to Ochsner Medical Center, New Orleans, LA, for evaluation of treatment options. We review current knowledge on this rare disease and data on modern treatment methods.

INTRODUCTION

Dercum's disease (DD) is a rare lipodystrophy syndrome characterized by obesity and tender fatty tissues. It is also known as adiposis dolorosa, lipomatosis dolorosa, Anders' syndrome [1], adiposalgia, adipositas dolorosa, adipose tissue rheumatism, lipalgia, and neurolipomatosis [2]. The fatty tissue growths in DD are classically distributed in the extremities, the trunk, the pelvic region, and the buttocks [3,4]. In addition to obesity and chronic pain, patients may develop a constellation of symp-

toms including fatigue, weakness, easy bruising, sleep disturbance, dyspnea, joint pain, and neuropsychiatric symptoms including emotional instability, depression, epilepsy, confusion, and dementia [4,5]. DD is frequently associated with metabolic derangements, such as diabetes [6], dyslipidemias leading to early atherosclerosis [6,7], and non-alcoholic fatty liver disease [8]. While such derangements commonly present in DD, they have not been etiologically linked and are common features in obese patients.

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Abbreviations: DD, Dercum's disease; MSL, lipomatosis; FML, familial multiple lipomatosis; FREMS, transcutaneous frequency rhythmic electrical modulation systems; NSAIDs, non-steroidal anti-inflammatory drugs.

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Though most cases occur sporadically, DD exhibits autosomal dominant inheritance with variable penetrance [4]. While both the epidemiology and etiology of this disease are poorly understood, the disease exhibits a female to male ratio as high as 30:1 [6].

Dercum's disease (DD) is an under-recognized and under-treated etiology of chronic pain and may lead to long-term debility. Etiologies of chronic pain may be difficult to resolve, and many including Dercum's disease are often associated with psychosomatic symptoms that may conflate the diagnosis with any number of chronic pain syndromes including fibromyalgia. For example, there is considerable difficulty in distinguishing DD with fibromyalgia in patients who are obese [7]. Consequently, the true prevalence of Dercum's disease is likely to be significantly under-estimated.

CASE PRESENTATION

A 47-year-old female with hypertension and DD diagnosed in 2014 presented to Ochsner Medical Center Clinic for recommendations on therapeutic options to treat her chronic pain.

Her symptoms began in 2011 with weight gain and tender lipoma formation in her upper and lower extremities. Back then, she had achy, whole-body pains which lasted days. She felt that back then her flares were monthly. She had a history of steady weight gain from 180 pounds in 2006 to 217 pounds in 2011. Additionally, in 2011 she had an excisional biopsy of an 8x10 millimeter mass in her left upper arm and was diagnosed with benign lipoma. That year, she also had an ultrasound of her left and right upper arms demonstrating many well circumscribed hyperechoic nodules bilaterally, with the largest measuring 1cm in diameter. The final reading was consistent with multiple fat necrosis. Additionally, this patient had been offered to enter a trial evaluating thermogenic agents in DD but ultimately declined.

At this visit, she presented with complaints of intermittent pains involving her whole body, and numerous small, tender lipomas in her upper and lower extremities. Her pains were achy and dull, with 10/10 severity, beginning spontaneously and evolving within a few hours and lasting several days. She experienced these pains twice this year and had intermittent episodes for eight years. She found that hot water immersion of her limbs and herbal detox regimens improved her pain. Her pain was worsened by consumption of sugary or fatty foods, exercise, and stress. These flares were associated with mild confusion, impaired memory, weakness, fatigue, and night sweats. She felt that flares were triggered by unhealthy eating, weight gain, and exercising, and she had undergone extensive lifestyle modification to eliminate these factors. In addition, flares typically began 3-4 days

before her menstrual cycle started. When flares were not related to her cycle, she felt she could predict their onset a day prior. She tried meloxicam 3.75 mg, which had improved her pain. She had previously been treated with prednisone 20 mg for one day, followed by 10 mg per day for 2 days. She was also prescribed additional prednisone for use as needed, but she felt that it did not help with her flares. Her last intramuscular injection of steroids was 1 year ago, and her last dose of oral prednisone was 3 years ago. She had since refused steroids. She tried ibuprofen 800 mg and gabapentin 100 mg, which did not help. She never used lidocaine, methotrexate, infliximab, or interferon.

Review of symptoms was significant for low grade temperatures to 99 degrees and night sweats twice a week, with the need to change her nightgown. She had chronic fatigue and body aches. She had dyspnea on exertion, easy skin bruising, and chronic dry mouth. She denied any joint stiffness or swelling.

Medical history was significant for hypertension on losartan 50 mg. She had chronic dry mouth, depression, and fibroids. She had a miscarriage in 1993 at 3 months gestation, complicated by retained fetal contents. Surgical history was significant for a hernia repair, cesarean section, and appendectomy. Family history was significant for a father with severe obesity. Her father weighed more than 400 pounds but was thin before his 30s. Per the patient, her father had similar pain flares. He had early and severe osteoarthritis. Her mother had rheumatoid arthritis and was undergoing treatment. Her maternal grandmother had similar arthralgias to her mother but was never diagnosed with a medical condition. The patient never smoked, did not drink, and did not engage in non-prescription drug use. She was employed in a stressful occupation in social work in the mental health setting.

This patient's blood pressure at this visit was 145/88. She had fluctuating hypertension with blood pressures between 168/91 and 117/76. Pulse rate was 76. Height was 5'3", with weight at 219 pounds, and BMI of 38.74. Physical examination showed a well-appearing obese woman who had some difficulty with remote memory. Cardiopulmonary examination was normal. Musculoskeletal exam revealed multiple sub-centimeter lipomas palpable which were very tender to light touch. These were not visible on general inspection. There were 7-8 nodules on the volar surfaces of left and right forearms, upper arms, and distal lower extremities. One large 2-3cm lipoma was present on the right forearm dorsal surface. This patient did not have tenderness in the shoulders, neck, and upper back.

Her laboratory values during initial evaluation demonstrated chronic hypokalemia between 3.2 to 3.8 (normal 3.5-5.1 mmol/L). Her last inflammatory markers had an elevated CRP at 17 (normal 0.0-8.2 mg/L) and elevated ESR at 30 (normal 0-20 mm/hr). Anti-nuclear

antibody, rheumatoid factor, and anti-cyclic citrullinated peptide were negative. Anti-SSA was not performed. CPK and TSH were normal. Vitamin D was low at 14 (normal 30-96 ng/mL). She had chronic iron deficiency anemia secondary to heavy menses and a colonoscopy without malignant findings. Follow up laboratory results showed continued microcytic anemia with hemoglobin 9.4 (normal 12.0-16.0 g/dL), borderline low potassium at 3.5 and low vitamin D at 24. Additionally, follow up CRP, ESR, CPK, aldolase, TSH, and free T4 were normal.

This patient's presentation remained consistent with DD, as she exhibited the cardinal symptoms of generalized obesity, multiple painful fatty masses, weakness and susceptibility to fatigue, and confusion. Cushing syndrome was considered due to hypokalemia, hypertension, easy skin bruising, weight gain, muscle aches, and fatigue. Vitamin D deficiency was considered in the differential due to fatigue and body aches. At her prior visit, family history of paternal obesity and pain was not known. Lipomatosis such as multiple symmetric lipomatosis (MSL) and familial multiple lipomatosis (FML) were considered less likely due to tenderness of subcutaneous nodules. Fibromyalgia was considered less likely due to absence of tender points.

This patient ultimately was referred to endocrinology to evaluate for Cushing syndrome. The patient was discharged with instructions to take meloxicam prior to flare to determine if it has abortive or suppressive effects. Clinic follow up was scheduled for 1 month pending evaluation of therapeutic options.

DISCUSSION

It is important for general practitioners and internists to have knowledge of DD, as well as its broad differential diagnoses to ensure such syndromes are appropriately recognized in the outpatient setting. Early recognition and evaluation are necessary to initiate treatment and referral to appropriate subspecialties, reduce stigmatization, and ultimately improve quality of life. Our patient, like many, presented with non-specific symptoms such as obesity, chronic episodic pain, fatigue, exercise intolerance, and easy bruising. DD should be considered when patients with similar symptoms present in an outpatient setting.

There have been multiple proposed classifications of DD since 1900. Most recently, Hansson et al. proposed that DD may be classified into generalized diffuse, generalized nodular, localized nodular, and juxta-articular subtypes [4]. Herbst et al. have reported three types: juxta-articular, diffuse generalized, and nodular [8]. Nodular forms involve formation of numerous tender lipomas, sometimes in the absence of obesity. Diffuse forms do not have palpable nodules. Objective diagnostic criteria have not yet been validated, and DD is a clinical

diagnosis of exclusion. There is no objective criterion for how many lipomas are required to describe a condition of lipomatosis. Historically, Roux and Vitaut first described four cardinal symptoms: painful fatty masses, generalized obesity, generalized weakness, and neuropsychiatric manifestations [4]. It remains unclear which of these are major or minor symptoms [2]. Hansson et al. proposed two minimal criteria: generalized overweightness or obesity, and chronic pain in adipose tissue lasting at least 3 months [4].

DD is frequently associated with metabolic derangements. Diabetes is present in approximately 16% of patients with DD [6]. Other reported metabolic derangements include dyslipidemias. Szygula et al. reported a DD patient with hypercholesterolemia leading to early atherosclerosis [9]. Similarly, Izar et al. reported an 8-year-old female with DD exhibiting low HDL-cholesterol, hyperinsulinemia, hyperbetalipoproteinemia, and predominance of small-dense LDL and HDL particles. Such lipid profiles characterize an insulin resistant state and are associated with progression of atherosclerosis. [10]. Unsurprisingly, DD is also associated with non-alcoholic fatty liver disease, most likely due to dyslipidemia [11]. While such associated conditions are commonly present in DD patients, they have not been linked etiologically directly to DD and are common features in obese patients.

In this patient, we describe diagnostic challenges and overlap between similar syndromes. The patient in this case presented with obesity, chronic episodic pain, and formation of multiple tender lipomas. She had associated fatigue, exercise intolerance, and easy bruising. Additionally, this patient had worsening symptoms during her menstrual cycle, with exercise, and with cold exposure. These symptoms were all consistent with a survey conducted by Herbst of patients with DD [3]. However, such symptoms are not specific to DD. Differentials for the above symptoms include fibromyalgia, endocrine disorders, primary psychiatric disorders, panniculitis, liposarcoma, and other lipomatosis syndromes [4]. Such syndromes include lipedema, MSL, and FML [6]. While endocrine disorders, panniculitis, and congenital neurofibromatosis syndromes could be diagnosed via biopsies and lab results, separating DD from lipomatosis syndromes has historically been difficult, particularly with lipedema, MSL, and FML [8].

Lipedema, also called lipoedema, is a rare disease involving edema and abnormal deposition of fat. Like in DD, lipedema exhibits female predominance, autosomal dominant inheritance, tenderness, abnormal fatty tissue distribution, and susceptibility to bruising [6]. Fatty tissue distribution classically involves the lower extremity, and patients may have associated gynoid obesity. The arms are involved in 30% of patients [6]. While discrete tender nodules are typically not palpable, examination of

subcutaneous adipose tissue may reveal tender pea-sized or “beanie baby” like nodules [8]. Elevating limbs does not improve lipedema. Compared to DD, patients with lipedema had a significantly lower prevalence of diabetes, at 6%, and less average daily pain [6]. Diagnosis is made clinically, based on symmetric lower extremity distribution of fatty tissue, pain, tenderness, and easy bruising.

DD and lipedema are occasionally confounded in the literature. While they are categorized as distinct conditions, reports refer to both lipedema and DD as *adiposis dolorosa*, leading to ambiguity in literature review [4,6]. Patients may have comorbid lipedema and DD [6]. Further, studies occasionally group DD and lipedema together when performing clinical trials and reviews. If there are no discrete tender nodules, the clinical differentiation between DD generalized-diffuse subtype and lipedema is subjective and is determined by distribution of fatty tissue and pain.

MSL, also known as Madelung syndrome and benign symmetric lipomatosis of Launois-Bensaude, involves multiple growths of fatty tissue. These accumulations are symmetrical and typically not painful [4,8]. Incidence has been proposed to be 1 in 25,000 [8]. MSL differs from DD as fatty tissue typically accumulates around the neck, upper extremities, and trunk. It usually presents in non-overweight patients, but in overweight patients it has been commonly mistaken for simple obesity [12]. MSL exhibits male predominance at a ratio as high as 30:1 [13]. Additionally, 88% of patients had history of moderate to heavy alcohol use [12]. MSL has been categorized into three types: type I involving the head, neck, and back, type II involving the body and proximal extremities, and type III involving the thighs and is more common in women. It is not associated with distal limb involvement except in females [8]. Most cases are sporadic, but MSL is associated with an A to G mutation of A8344 in mitochondrial DNA and is thought to exhibit mitochondrial inheritance as well [4,6]. This mutation is present in less than half of patients [8]. This mutation has not been found in DD [4]. MSL is a clinical diagnosis based on demographics, family history, and distribution of excess fat accumulation around the neck, head, and upper torso alone [4]. The distinction between DD and MSL type III is subjective and based on tenderness of fatty masses, presence of obesity, and limb involvement. Many case reports involving DD are misdiagnoses of MSL [4,8].

FML is considered a separate condition from DD and MSL [4]. It is rare with an incidence of 0.002%, demonstrates autosomal dominant inheritance, and may be associated with a mutation on chromosome 12 affecting the protein Isoform I-C [12]. It has increased prevalence in men at up to 76% of cases [6]. Compared to MSL, FML has fewer occurrences in the neck and shoulders [12]. Bi-

opsy demonstrates benign morphology but plays a role in ruling out malignancy. Diagnosis is clinical and is based on multiple lipomas and significant family history.

DD and FML are also frequently reported together, however whether these are distinct diagnoses is unclear as both conditions involve lipomas in similar distribution and familial inheritance. Additionally, patients may have concomitant DD or lipedema with FML [6]. No mutations in cases of inherited DD are identified yet [4]. It has been suggested that DD nodular type may be a subset of FML, as the primary clinical difference is presence of tenderness [4,8].

Further research is needed to fully categorize these rare overlapping conditions and validate objective criteria for diagnosis. Due to DD’s inheritance pattern and possible association with FML, genetic testing may play a role in the future of the diagnosis of this disease. This present patient has a possible positive family history of father to daughter transmission.

CURRENT MANAGEMENT OF DERCUM’S DISEASE

Current DD management focuses on symptomatic treatment, as there is no effective cure due to its elusive pathogenesis. There are no FDA approved DD treatments, and current treatments are based on individual case reports and small series of patients. However, such studies and reports have shown that surgical and medical treatment can provide pain relief. Hansson et al., have shown that liposuction can slightly improve the quality-of-life in DD patients [14] and has been well tolerated with minimal thermal or vibratory sensory changes [15]. Moreover, dermolipectomy has been used as a treatment in case reports albeit with little studies done on its effectiveness and disease recurrence [16,17]. Besides surgical intervention, other procedures shown to symptomatically improve DD include transcutaneous frequency rhythmic electrical modulation systems (FREMS) [18] and intensive tissue massage therapy [19].

On the other hand, medical treatment focuses on analgesia. Traditionally, DD has most commonly been treated with non-steroidal anti-inflammatory drugs (NSAIDs) or narcotics, other medications include topiramate, tramadol, lidocaine patches/gel, intravenous lidocaine, methadone, gabapentin, pregabalin, tricyclic antidepressants, ziconotide, and ketamine [3]. Immunosuppressants such as methotrexate, infliximab [20], interferon alpha-2a [21], and corticosteroids [22] have also been used. Surprisingly, metformin has been shown to improve pain symptoms in DD patients with type 2 diabetes mellitus [23] by a yet unknown mechanism. As many DD patients have a high risk of developing non-alcoholic fatty liver disease, a recent report showed that d-amphetamines decreased

liver lipid deposition in two patients [11]. Recently, Wipf et al. showed in one patient that intralesional injection of deoxycholic acid, an FDA approved therapy to reduce submental fat, successfully reduced the pain and size of the lesion subjectively [24], suggesting a less invasive alternative to liposuction. DD continues to be a painful disease which significantly decreases the quality of life in many patients, thus more clinical studies must be done to standardize both surgical and medical treatment of DD.

The first randomized, double-blinded clinical trial for minimally invasive treatment of DD is currently ongoing. RZL-012 is a small molecule drug by Raziol Therapeutics which may induce fibrosis of adipose tissue following intralesional injection [25]. It is proposed that RZL-012 attracts circulating fibrocytes to differentiate into myofibroblasts, causing fat to become a “myofibroblast trap” resulting in local inflammation and replacement of adipose tissue by fibrosis [25]. In a phase 2a clinical trial to evaluate RZL-012’s drug safety profile reported no significant adverse effects (NCT03171415), and reduction of lipoma height by 50% and pain by 70% in DD patients [26,27]. The FDA have also designated RZL-012 as an orphan drug for the treatment of DD in November 2019 [26,28]. Currently, a Phase 2b clinical trial to evaluate RZL-012’s efficacy has been completed in January 2020 (NCT04229030) with results yet to be released [29]. While these results are preliminary and many studies remain to be done, it will be exciting to follow if RZL-012 will become the first FDA-approved drug for DD treatment.

CONCLUSION

DD is a rare condition involving obesity, tenderness, and formation of fatty deposits. Diagnosis of this disease is difficult and frequently missed, leading to reduced quality of life. Further, clinical differentiation from a family of similar rare adipose disorders is challenging due to significant overlap in symptomatology, disease behavior, and inheritance patterns. Further research is needed to validate objective criteria to diagnose these rare conditions and determine an etiology.

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