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### DERCUM'S DISEASE: AN OVERVIEW OF CLASSIFICATION, CLINICAL PRESENTATION, DIAGNOSTIC CRITERIA AND MANAGEMENT

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#### ABSTRACT

Dercum's disease is a rare disorder described by generalized obesity with painful adipose tissue. The clinical symptoms presented were multiple painful fatty masses, fatiguability, swelling of fingers, morning stiffness, cognitive dysfunction, headache, anxiety, rapid heartbeat, shortness of breath, bloating, constipation, easy bruisability, joint aches, muscle aches, mood swing, delirium and dementia. Dercum's disease affects women more frequently than men. Elevated erythrocyte sedimentation rate, alpha-1 antitrypsin, orosomucoid, haptoglobin, compliment factors C<sub>3</sub>, C<sub>4</sub>, Clq and Cl<sub>s</sub> have been found in Dercum's disease. Differential diagnosis includes Fibromyalgia, Madelung's, Familial multiple lipomatosis, Proteus syndrome, Weber-Christian disease, Neurofibromatosis type 1, Frohlich syndrome, Lipodystrophia and Metabolic disorders. The diagnosis is made clearly when the differential diagnoses have been excluded. The main goal of treatment in Dercum's disease includes the pain reduction with surgical interventions (liposuction, excision), pharmacological therapies (analgesics, membrane stabilizing agents, corticosteroids, calcium channel modulators, methotrexate and infliximab, Interferon  $\alpha$ -2b) and other alternative such as Rapid cycling hypobaric pressure and Frequency Modulated Electromagnetic Neural Stimulation. We propose a review on definition, classification, pathophysiology, diagnostic methods and treatment.

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## INTRODUCTION

In 1888 Francis Xavier Dercum, an American neurologist describes Dercum's disease, also known as adiposis dolorosa, lipomatous dolorosa, morbus dercum, adipose tissue rheumatism, adipsalagia syndrome, Ander's syndrome or Dercum-vitaut, fatty tissue rheumatism as a rare progressive disorder with an unknown cause.[1, 2, 3] The disease was characterized by multiple painful subcutaneous lipomas on the trunk and extremities.[4,5] Dercum's disease affects women more frequently than men, especially during middle age (35-50 years).[6] Contrary many studies suggest that even though it affects in different ages; most commonly occurs in post-menopausal women.[7] The prevalence of Dercum's disease has not established yet now. Dercum's disease is suggested as an autosomal dominant inheritance disease which is characterized by multiple asymptomatic lipomas. [8]

## PATHOPHYSIOLOGY

Pathogenesis and mechanism of Dercum's disease is not well understood. The origin of pain may be due to the fatty deposit which causes nerve compression and leads to weakness. Some authors suggest the pain is originated and developed by the sympathetic nerve stimulation. [9] In some studies, the Dercum's disease associated with a defect in the synthesis of monounsaturated fatty acids. [10] On analyzing the genetic basis of Dercum's disease, the previous studies suggests it as an expression of familial multiple lipomas, with variable phenotypic expressivity, ranging from asymptomatic to extremely painful lipomas.[8]

## CLINICAL PRESENTATION

Dercum's disease is multilesional rather than single lesion. Pain associated with subcutaneous lumps is the main symptom of Dercum's disease. [11]The pain is temperature and weather dependent. The most commonly affected area includes the extremities, the trunk, the pelvic area and the buttocks. [12] The disease were associated with weight gain/obesity along with chronic pain for more than 3 months.[13 ] Severe obesity may finally leads to fatigability and weakness in patients with Dercum's disease. Central nervous system disturbance such as mood swing, delirium, dementia and epilepsy may also occur. Pain is mainly presented as burning, aching or smarting sensation.[14] According to Roux et al. the four cardinal symptoms demonstrated in Dercum's disease are:- (1) multiple, painful, fatty masses (2) generalized obesity (3) weakness and fatigability and (4) mental disturbances.[15] Other symptoms includes swelling of fingers, morning stiffness, cognitive dysfunction, headache, anxiety, rapid heartbeat, shortness of breath, bloating, constipation, easy bruisability, joint aches and muscle aches.[12]

The mechanism involved in occurrence of pain may be due to the pressure exerted in the nerves by growing fatty masses, inflammation and autoimmune problems. [11, 15, 16] The neuropathic pain has been suggested to be caused by the abnormal connections between autonomic and sensory nerves in the periphery which results in abnormal autonomic signaling to the spinal cord which activates the pain fibers. [17]

## CLASSIFICATION

In 1900, Giudicaendra[18] classified Dercum's disease as:-

- 1) Nodular Type: Painful lipomas, which most commonly occurs on the arms, legs, back or on the thorax or in the multiple locations. The nodules may be variable in size and painful.
- 2) Diffuse Type: The type in which diffusely painful (symmetric) adipose tissue is present.
- 3) Mixed Type: A uniform with both diffusely painful adipose tissue and painful nodular masses were present.

Roux et al.suggested another classification as:(i) Nodular type (ii) Circumscribed diffuse type (located inside of the knee and/or on the hips), (iii)Generalized diffuse type (located in the extremities and the trunk). [19] Later, another classification was established [20-22]:-

- i) Type I-Juxta-articular ii)TypeII-Diffuse generalized iii)Type III-Nodular

In typeI the localized accumulation of painful fat primarily occurs near joints (knee) and /or on the hip. The common symptoms associated with juxta-articular type are pain and impaired mobility. In typeII mainly occurs in the dorsal upper arm, dorsal folds, soles of feet, stomach wall, gluteal region and axillar region. A nodular multiple lipoma of approximately 0.5-4cm attached to the surrounding tissue describes type III. Based on a review of Dercum's disease conducted in 2012, the proposed classification is as follows[23]:-

- i) Type I (Generalized diffuse form)ii) Type II (Generalized modular form)iii) Type III (Localized nodular form)iv) Type IV (Juxta-articular form)

## DIAGNOSIS

Diagnosis of Dercum's disease is made by systematic physical examination as well as through exclusion of differential diagnosis. The laboratory investigations are non-specific. Certain active parameters show abnormality from their normal levels. Elevated erythrocyte sedimentation rate, alpha-1 antitrypsin, orosomucoid, haptoglobin compliment factors C<sub>3</sub>,C<sub>4</sub>,Cl<sub>q</sub> and Cl<sub>s</sub> might occurs in some cases of Dercum's disease.[24,25] Previous studies shows the monounsaturated fatty acid ratio is greater than that of saturated fatty acid.[26] Another study suggests the occurrence of a metabolic block in the synthesis of lipids.[10] Some studies shows that the ultrasonography and magnetic resonance imaging may be useful as a supportive in diagnosing fatty tissue inflammation. The sonographic findings in Dercum's disease vary from those of simple lipomas which are larger, not hyperechoic; multiple and not numerous as seen in Dercum's disease. In case of magnetic resonance imaging, the simple lipomas determine only facts signal which differs in Dercum's disease. [11]

### Differential Diagnosis

The differential diagnosis should be excluded before diagnosing Dercum's disease. The differential diagnosis of Dercum's disease is shown in table 1.

Fibromyalgia is characterized by pain (gradual /sudden onset) throughout the body muscle and abnormally persistent episodes of fatigue. The other symptom occurs are muscles spasms, stiffness, sleep disturbances, cognitive disturbances and depressive symptoms. [27]

Madelung's disease (benign symmetrical lipomatosis) is a condition in which metabolism (breakdown of fats).The fatty deposits are seen around the neck, shoulders, upper extremities (upper arms and upper back). Mostly affected population is alcoholic adult male; even though women and non-alcoholics can also develop Madelung's disease.

Proteus syndrome includes lipomas with partial gigantism of the hands or feet, hemihypertrophy, pigmented nevi, other subcutaneous neoplasms.

Familial multiple lipomatosis is a rare disorder affecting the arms and legs by the formation of multiple benign masses or lipomas. The disease is an autosomal dominant trait and occurs usually during adolescence. [28] The remaining differential diagnosis is listed in table 3.

**Table 1: Differential Diagnosis of Dercum's Disease.**

<b>Fibromyalgia</b>
Madelung's (benign symmetrical lipomatosis, Lanois Bensaudes syndrome)
Familial multiple lipomatosis
Proteus syndrome
Weber-Christian disease
Neurofibromatosis type 1
Frohlich syndrome
Lipodystrophia progressive
Metabolic disorders (Cushing syndrome, Hypothyroidism)
Cowden's disease
Myoclonus epilepsy with red ragged fibers (MERRF)
Congenital lipomatosis
Erythema nodosum
Primary psychiatric condition (Depression)
Erythema induratum
Multiple endocrine neoplasia I (MEN1)

### MANAGEMENT OF DERCUM'S DISEASE

Dercum's disease treatment focuses on symptomatic control which can be either medical or surgical. Non-pharmacological treatment modalities such as acupuncture, cognitive behavioral therapy, hypnosis and bio-feedback may be used as adjuncts to pharmacologic treatment. [29]

#### Surgical Therapies

Surgical therapies for the treatment of Dercum's disease include: - lipoma resection (surgical excision of isolated lipomas) or liposuction. [4] Liposuction is the removal of adipose tissue. Liposuction is found to be supportive care treatment to relief from the pain associated with the disease and improves the quality of life. In case of fibromyalgia or when shown with swelling and recurrent lipoma flare-up, liposuction is not indicated. [30,31] The surgical intervention with liposuction leads to destruction of nerve plexus offered in the adipose tissue.[32]

#### Pharmacological Therapies

##### Analgesic and Non-Steroidal Anti-Inflammatory Drugs

The traditional pharmacological treatment of Dercum's disease includes local and systemic analgesics as well as non-steroidal anti-inflammatory drugs. The previous studies show that the use of analgesics and non-steroidal anti-inflammatory drugs decline the pain by 89% and 97% respectively. [12] However lipomas are sometimes unresponsive to analgesics and non-steroidal anti-inflammatory drugs. In certain cases opioids may be used to relieve the patient from pain. [32] Acetaminophen combined with an opioid analogue is the first line drug of choice.

### **Membrane Stabilizing Agent**

Membrane stabilizing agents such as Lidocaine and Mexiletine has been used to provide pain relief. Intravenous Lidocaine 200-400mg over 15 minute on every – other - day dosing gets rid of the pain for 10 hours to several months. But the studies report that the patients administered with doses of 200-400mg presented with euphoria, numbness during infusion, flushing and altered mental status.[33] Atkinson in a study described 2-12 months of pain relief with Lidocaine infusion for a period of 2 year.[34] Serious side effects such as cardiac toxicity and seizure have been reported with the administration of 1300mg Lidocaine in a duration of four days.[35] Lidocaine acts as a pain reliever by blocking the impulse conduction in peripheral nerves and also by depressing the cerebral activity. Siriki et al. recommends the efficacy of transdermal Lidocaine (5% patch) in treatment of neuropathic pain related to Dercum's disease. [3]

Mexiletine (Class I B Anti-arrhythmic), an analogue of Lidocaine gives long lasting pain relief with the oral treatment. The pharmacokinetic of Mexiletine varies with Lidocaine i.e., it metabolizes less rapidly than the Lidocaine and proven to be effective even in patients who are not responding to intravenous Lidocaine therapy. [36,37]

### **Corticosteroids**

Corticosteroids such as Prednisone, Methyl prednisolone shows an extreme improvement in patient. Corticosteroid reduces the pain by inhibiting the pain modulators such as serotonin, histamine, prostaglandins and bradykinin. [38]Prednisone 20mg daily has been used to provide pain relief. In some cases, high dose of corticosteroids were found as an induction of disease. [39]

### **Calcium Channel Modulators**

Calcium channel modulators such as Pregabalin, primarily used in treating neuropathic pain act by inhibiting neuronal calcium channel activation; thereby blocks the release of excitatory amino acids which are necessary for pain sensitization.[40]

### **Interferon $\alpha$ -2b**

Interferon  $\alpha$ -2b shows long term relief of pain in Dercum's diseases. The mechanism which relieves the pain by Interferon  $\alpha$ -2b remains unclear. The authors explain as it may be related to its anti-viral effects, to the production of endogenous substances or by the interference of Interferon with interleukin and tumor necrosis factor, alpha cytokine production. [41]

### **Methotrexate and Infliximab**

Methotrexate and Infliximab delivers permanent pain relief in patient Dercum's disease. Both reduce the neuropathic pain caused peripheral nerve injury.

### **Metformin**

Recently, Metformin had been used successfully in patient with Dercum's disease associated with pain. The drug act by altering the cytokine milieu, impacting mediators such tumor necrosis factors, interleukin -1 and leptin.[42]

### **Other Alternative Treatments**

#### **Rapid Cycling Hypobaric Pressure**

The cyclic variation in altitude conditioning is a method of touch free cyclic hypobaric pneumatic compression for the treatment of tissue edema and associated pain. In Dercum's disease hypobaric compression may decrease tissue fluid and improve the oxygen saturation there by resulting in the decreased pain.[43]

#### **Frequency Modulated Electromagnetic Neural Stimulation(FREMS)**

FREMS, a novel transcutaneous electrotherapy compressed of a sequence of modulated electrical stimuli automatically different as for pulse frequency, duration and voltage amplitude. FREMS result in significant reduction in pain, decreased subcutaneous adipose tissue thickness and fat and thus improves the health status of patient. The mechanism of FREMS treatment was unclear. According to previous study reports FREMS treatment increases microvascular blood flow, enhance vasomotor activity of smooth cells, releases vascular endothelial growth factors and changes the amplitude of Hoffmann reflex. [6]

### **CONCLUSION**

Dercum's disease presented with multiple fatty subcutaneous lumps characterized by pain is a rare disorder with unknown etiology. The diagnostic modalities of Dercum's disease need to be checked out. The treatment strategy includes supportive therapy and symptomatic relief of pain.

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## REFERNCE

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