aesthetic medicine

Review

Dercum's disease or Adiposis Dolorosa: a complex condition still awaiting full definition

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Short title: Dercum's Disease or Adiposis Dolorosa

Abstract

Dercum's disease (DD), also called adiposis dolorosa (AD), is known as a rare, chronic and progressive disorder characterized by multiple, subcutaneous painful adipose tissue masses. DD mainly occurs in overweight or obese adults, mostly post-menopausal women. Pain, which can be severe and often debilitating, is frequently, but not always, associated with generalized weakness and mental disturbances. Other associated symptoms are also recorded but are not common in all cases diagnosed as DD. To date, the etiology remains indefinite and the basis of the pain is not yet clear. Thus, DD is mainly described for its symptoms rather than for the pathophysiological process. In sporadic cases, the condition has been reported to be inherited as an autosomal dominant trait. To date, treatment is still symptomatic and includes liposuction or surgery for the most painful fatty masses and analgesics to control pain. Nonetheless, the symptoms are often uninfluenced by conventional pain therapy. In the present review, we have retraced the most significant historical steps of research and study on DD, mostly highlighting the difficulties in defining pathophysiology, diagnosis and treatment which are mainly due to the wide variability of the findings and clinical signs in the cases described in the literature. The extremely complex picture that emerges should strongly stimulate to develop scientific studies aimed at identifying the etiologic factors of this devastating pathology that, with high probability, is not always recognized and, too often, neglected.

Keywords

Dercum's disease, adiposis dolorosa

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Historical notes

Adiposis dolorosa (AD) was first described in 1892 by the physician, philosopher, neurologist, scientist, Francis Xavier Dercum[1-4], from a case in the Philadelphia Hospital[5]. In this original paper, Dercum described 3 cases of the disease with the gross pathological findings of 2 cases, both of which showed abnormal thyroid glands, thus leading the neurologist to believe that the disease was a clinical entity on the basis of a "*disthiroydia*". This article was preceded by a case report by Dercum himself in 1888[6], as a 51 year-old woman of Irish heritage with severe pain and enlarged subcutaneous adipose tissue on her arms and back.

He wrote: "*Evidently the disease is not simple obesity. If so, how are we to dispose of the nervous elements present? Equally plain is it that we have not myxoedema to deal with. All of these cases lack the peculiar physiognomy, the spade-like hands, the infiltrated skin, the peculiar slowing of speech, and the host of other symptoms found in myxoedema. It would seem then, that we have here to deal with a connective tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or at best unevenly distributed and associated with symptoms suggestive of an irregular and fugitive irritation of nerve-trunks - possibly a neuritis... Inasmuch as fatty swelling and pain are the most prominent features of the disease, I propose for it the name Adiposis Dolorosa*".

Dercum regarded the disease as a clinical entity and named it adiposis dolorosa (AD) because of its most characteristic symptom, painful fat.

In 1899 White[7] described an interesting case of AD as follows: "*My patient shrieks when she is gripped...my patient can hardly walk,...My patient goes out of her mind temporarily. Headache is a common symptom.*

Herpes, hematemesis, epistaxis, early menopause, slight pigmentation of the skin, atrophy of the muscles of the hand, and reaction of degeneration of them have all been described as occasional symptoms.

...In my case administration of thyroid did no good....She has been in several hospitals but all with no benefit".

The first clinical classification system for AD (also named Dercum's Disease, DD) was developed in 1900 by Giudiceandrea[8] as follows:

I. Nodular type.

A form with painful lipomas, most commonly on the arms or the legs or on the back or thorax. Sometimes the lipomas occur on multiple locations and occasionally the lipomas form a confluent mass.

The nodules are variable in size and painful on palpation.

II. Diffuse type.

A form with diffusely painful adipose tissue. The pain is symmetric.

III. Mixed type.

A form with diffusely painful adipose tissue and with painful nodular masses.

This classification was then revised in 1901 by Roux and Vitaut[9] which proposed four cardinal symptoms of DD, used as diagnostic criteria for several years[10-17]:

1. *Multiple, painful, fatty masses*
2. *Generalised obesity*
3. *Weakness and susceptibility to fatigue (asthenia)*
4. *Psychiatric manifestations, including emotional instability, depression, epilepsy, confusion, and dementia.*

What was reported by Burr in 1900[18], was then confirmed in 1902 by Dercum[19] who described two other cases of AD and considered the most interesting histological finding to be interstitial inflammation of the nerves in the adipose tissue of the painful sites. In the same year, Dercum and MacCarthy[20] published a case of AD with complete autopsy findings, the main pathological lesion being an "adenocarcinoma" of the pituitary body, while the thyroid appeared regular. Next, several cases were described, many of which showed abnormalities of the pituitary gland[21-24]. DD was also defined as a disorder of the "haemolymph" system by Dercum and McCarthy themselves[20] and "*a general disease of the lymphatic system*" by Mills[25], suggesting that dysfunction in the hemovascular and/or lymphatic systems may contribute to the development of lipomas. As early as 1910, Stern[26] noted that neuropsychiatric disturbances and asthenia did not accompany every case. Cushing in 1912[27] first questioned the rationale of calling the disease a clinical entity, stating that, in his opinion, many cases reported as AD, "*are actually examples of disturbed metabolism secondary to disease of the ductless glands*". In his later articles, Dercum appeared to be of the same opinion. In sections from DD adipose tissue increased levels of connective tissue were described by Myers in 1923[28]. In 1924 Purves-Stewart[29] classified the disease among the thropho-neuroses, probably due to disturbed activity of the thyroid and the posterior lobe of the pituitary body. Winkelman and Eckel in 1925[30] reported that the disease could be considered as a polyglandular disorder with a consequent altered fat metabolism. In the first decades of the 1900s several further cases of AD were described[31-39]. Moreover, Foot et al in 1926[23] described a case of AD with necropsy: "*The body is that of an extraordinarily adipose negress. …The necropsy findings coincide very accurately with those in undoubted cases of AD. The very definite lesions in practically all the endocrine glands are striking: pituitary sclerosis and hyperplasia, with a tumor; sclerosis and changes in the colloid content of the thyroid; persistent and well preserved thymic rests; adenoma of both suprarenals, with hyperplasia; ovarian sclerosis and atrophy; and definite, though slight, changes in the pancreas. Besides these, we see changes in the cranial bones, with exostoses and definite cerebral atrophy, with some generalized thickening of the dura. …. It is justifiable, however, to ascribe the pathologic findings in this case to a profound disturbance in the endocrine system, probably arising as a result of one of the lesions found in the hypophysis cerebri*". At the same time, Labbé and Boulin[40] reported a case of AD with psychic and nervous disorders which they could not attribute *to any one thing which could at the same time cause obesity.* These Authors questioned whether the weakness and susceptibility to fatigue and psychiatric manifestations should be classified as cardinal symptoms.

They argued that obesity per se can induce asthenia, and that it is unclear whether mental disturbances should be included as cardinal symptoms.

Gram in 1930[41] described a high incidence of obesity with tender subcutaneous infiltrations, "*deforming arthritis*" of the knee, and arterial hypertension in women around and after the climacteric age. Newburgh in 1931[42] pointed out that painful areas of fat could

disappear just by regulating diet. According to Wilson[43] the disease could be considered as "*really a syndrome of symptoms in obese people*" and "*AD could not be a clinical entity since there have been no findings consistent in all the cases reported in literature*". He considered more reasonable to assume that the condition is one of either simple obesity or lipomatosis associated with neurosis or neurasthenia, and that the pathological conditions that had been found in these cases that have come to autopsy were incidental. A report by Boller in 1934[44] showed that intralesional injections of procaine relieved pain in six cases. Kling in 19374[5] reported on 112 cases of juxta-articular AD, their significance and relation to DD and osteoarthritis. Since then, four cases of juxta-articular DD in association with seropositive rheumatoid arthritis were reported[46,47]. Furthermore, Kling[45] came up with the theory that adipose tissue deposits around the knees might interfere by pressure on the joint with the blood supply and resulted in the development of painful osteoarthritis. In 1952 Steiger et al[48] expressed their doubts on the pluriglandular involvement in DD. Hovesen in 1953[11] reported the inflammatory signs in the DD adipose tissue, i.e. infiltration of leukocytes and plasma cells. The painful lipomas could appear in any location and, even if several adipose tissue diseases may present similarly, the pain of DD is specifically associated with fatty nodules[49-52]. The absence of pain of the adipose masses should indeed distinguish DD from Cushing syndrome, multiple symmetric lipomatosis, familiar multiple lipomatosis and lipedema as well as cutaneous malignant metastases[53-56].

In 2005 DD was unrelated with malignancy by Wortham and Tomlinson[52]. Gastrointestinal symptoms were also found to be associated in some DD patients[57,58] as well as metabolic complications including obesity, diabetes, hypertension, dyslipidemia, and nonalcoholic fatty liver disease[58,59].

Hereditary factors in DD have been reported by some Authors[53,60,61]; however, most reported cases of familiar occurrence of the condition was considered to be sporadic[62]. DD has been suggested to be an expression of familial multiple lipomas, which is an autosomal dominant disease characterized by multiple asymptomatic lipomas[63]. This observation was derived by studying the family patterns of 2 siblings with DD; findings suggested that the disease segregates in an autosomal dominant fashion with variable phenotypic expressivity, ranging from totally asymptomatic to extremely painful lipomas. Mutational analysis excluded the 8344A→G mitochondrial mutation seen in other patients with multiple lipomas[62,63]. The A→G transition at position 8344 in the tRNAlys gene of mitochondrial DNA has been described in the syndrome myoclonic epilepsy and ragged-red fibers (MERRF). The presence of multiple lipomas resembling those of multiple symmetrical lipomatosis had been described in some members of pedigrees with MERRF harboring the 8344 tRNA mutation[64]. An inflammatory etiology has been proposed for DD[65-67]. However, laboratory markers for inflammation markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were reported by some authors as normal in most patients[12,47,57-59,67-76]. On the other hand, a few studies revealed elevated levels of CRP and ESR, even if some patients were also affected by an autoimmune disease[58,75,77]. Commonly, markers for autoimmune disease, such as autoantibodies, are negative in DD[77-79]. A review of the histopathologic findings of DD showed no consistent histologic abnormality in the adipose tissue that might distinguish these tumors from common sporadic lipomas[80]. The involvement of hormones and neuropeptides as well as a low level chronic inflammation and vascular factors was discussed by Hansson et al in 2011[81]. In theory, the sudden appearance of the disease together with the incidence of a slight increase in the number of inflammatory cells in the fat pointed toward the disease being, in part, an immune defense reaction[76,82]. Herbst et al in 2009[83] reported that inflammation and excess collagen may contribute to lower relative resting energy expenditure in patients with AD. The authors observed significantly higher IL-6 as well as mononuclear giant cell levels in AD compared with control adipose tissue. The study on adipokines indicated that there was no difference in the levels of tumor necrosis factor (TNF)-α, leptin, adiponectin, plasminogen activator inhibitor-1, interleukin (IL)-1β, IL-8, IL-10, macrophage inflammatory protein (MIP)-1α, and monocyte chemotactic protein (MCP) compared to controls[83]. Nonetheless, significantly lower MIP-1β expression and a trend toward higher levels of IL-13 (interleukin-13) were reported. In addition, lower levels of fractalkine, also known as chemokine (C-X3-C motif) ligand 1, were seen. The authors concluded that the lowered fractalkine levels were logical, since with prolonged release of fractalkine as seen in neuropathic pain, the receptors to which fractalkine binds are upregulated. This suggests that there is shift from fractalkine release to receptor-bound fractalkine. The lower levels of fractalkine found in DD could thus suggest that the substance is receptor-bound. When receptors are occupied by fractalkine, pain and resistance to opioid analgesia are promoted.

Rasmusssen et al[84] discovered an abnormal lymphatic phenotype in three patients with the disease compared with four female controls using near-infrared fluorescence (NIRF) lymphatic imaging. The lymphatics in the participants with DD were intact and dilated but could not readily clear lymph when compared with lymphatics in four control patients. Further NIRF imaging revealed masses of fluorescent tissue within the painful nodules, suggesting a lymphovascular etiology. Kawale et al[85] presented a DD patient with painful thickening of the scalp in bilateral parieto-occipital areas and vertex for more than a year. The pain in the scalp caused headaches and disturbed sleep and daily activities. CT and MRI revealed diffuse thickening of the scalp tissue, but no evidence for other anomalies. Tsang et al[86] noted a case of DD that caused weight loss failure after Roux-en-Y gastric bypass. Eighteen months after the operation the patient was unable to lose weight, despite adherence to behavioral and dietary guidance. Endoscopy performed 15 months after the operation excluded that any complications had occurred. Dercum patients often report that their obesity is refractory to diet and exercise intervention. Nonetheless, this has never been studied.

Hao et al (2018)[87] have recently described an interesting case of a 39-year old man with trauma induced DD. The

authors in their report highlighted the rare nature of painful adipose deposits and the diagnostic challenges. On histopathology, the fat deposition in DD was notable for mature adult fatty tissue and sometimes, a number of blood vessels suggesting an angiolipoma.

According to some reports, ultrasonography and magnetic resonance imaging (MRI) may aid in the diagnosis of DD[74,88,89]. In the study by Tins et al[88] on 13 patients with DD, lesions of the condition were found to be markedly hyperechoic on ultrasound, superficial in location, and distinct from characteristic lipomas. Further, when validated on more than 6000 MRIs, they appeared as ill-defined, nodular, "blush-like" subcutaneous fat on unenhanced MRI with a decreased T1-weighted signal. No case of DD was without these features in the study, and the authors concluded that these findings, along with multiple subcutaneous fatty lesions, is "very suggestive and possibly pathognomonic" for the condition. In regards to the pain treatment in DD, some improvement was reported after systemic or intralesional treatment with corticosteroids[47,80,90,91], whereas others experienced worsening of the pain[92]. According to Taniguchi et al[93], the alterations of fat metabolism induced by corticosteroid excess could play a role in the development of this syndrome. An earlier study suggested that a defect in the synthesis of monounsaturated fatty acids may play a role in its development[12]. Further studies are needed to support this hypothesis and to identify a specific biochemical defect. Dalziel[94] suggested that the autonomous nervous system mediates pain in DD. Vasoconstrictor response could be normalized by lidocaine infusion that is thought to decrease the local or central sympathetic vasoconstrictor tone. Nonetheless, any substantial evidence of nervous system dysfunction has never been found in DD and is hence merely a theory.

Gonciarz et al[95] reported in 1997 that interferon (INF)-alfa-2b induced long-term relief of pain in 2 patients with AD and chronic hepatitis C. The analgesic effect of IFN therapy occurred 3 weeks after treatment for 6 months. Whether the mechanism of pain relief with IFN is related to its antiviral effect, to the production of endogenous substances, or to the interference of INF with cytokines involved in cutaneous hyperalgesias, i.e. interleukin 1 and tumor necrosis factor-alpha, remains still undefined. Two DD case reports have described pain relief with daily intake of mexiletine, an antiarrhythmic[70,96]. Traditional analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), had been thought to have a poor effect, with the pain in DD often refractory to analgesics and to non-steroidal anti-inflammatory drugs (NSAIDs)[44,46,68,77-79,91-100]. However, in their extensive article published in 2007, Herbst and Asare-Bediako concluded that 89% achieved relief when treated with an NSAID, as did 97% when treated with an opiate[58]. In the same year, Singal et al[101] reported improvement of a DD patient on infliximab, with and without methotrexate. In 2008, Desai et al[102] reported on successful treatment with a lidocaine (5%) patch, and Lange et al[69] on one with pregabalin associated to manual lymphatic drainage. Metformin was used with success for AD associated pain by Labuzek et al[103]. It was hypothesized that the drug could favorably alter the cytokine profile, impacting on tumor necrosis factor, interleukin–1, and leptin[104,105]. The pilot study of Herbst and Rutledge[105] suggested that rapid cycling hypobaric pressure might reduce pain in patients with DD. Nonpharmacological approaches for DD may be used as adjuncts to pharmacologic treatments. Some of these include acupuncture, cognitive behavioral therapy, hypnosis, and biofeedback[68,106]. Several liposuction treated patients were reported by Hansson et al in 2011[107]. According to Dalziel the mechanism behind pain relief following liposuction was nerve plexus destruction within the adipose tissue[94]. However, Hansson et al retained unlikely that direct nerve destruction alone explained the pain reduction seen following liposuction[107,108]. Liposuction is regarded as a supportive treatment for DD. Any skeletal pain is not affected. A significant initial reduction of pain and an improved quality of life is seen but these effects decrease over time[109].

Dercum's disease still looking for clear and definitive answers

In an extensive review published in 2012 based on literature data and studies concerning 111 DD patients[81,107,108], Hansson et al[56] described the classification, symptoms and diagnosis, as well as, the epidemiology, etiology, genetic counselling, treatment and prognosis of the disease. They discussed which symptoms were cardinal and which were associated and promoted a "minimal definition" of AD which including the following signs:

- *Most often generalized overweight or obesity*
- *Chronically painful adipose tissue (>3 months)*

These authors also suggested the following classification system:

- *Type I: Generalized diffuse form; generalized, widespread painful adipose tissue in the absence of discreet lipomas*
- *Type II: Generalized nodular form; widespread painful adipose tissue with concomitant intense pain in and around multiple discreet lipomas*
- *Type III: Localized nodular form; pain in and around multiple discreet lipomas*
- *Type IV: Juxta-articular form; discreet deposits of excess fat in specific locations, including the medial aspect of the knee, the hips, and, rarely, the upper arm.*

Hanssen et al[56], by retracing many cases described in the literature, analyzed the consistency between the clinical signs reported and the minimum criteria for the diagnosis of DD. With the exception of a few cases[110], according to the authors most of the analyzed literature cases[67,72,85,104,111-114], were not fully consistent with the minimal diagnostic criteria.

Since the original description of DD, in addition to the painful nodular fatty deposits (which are often unaffected by weight loss), the clinical spectrum has changed to include to various degrees other components of DD[58] i.e. general obesity, easy fatigability and weakness (asthenia), and a wide variety of unexplained emotional disturbances, such as depression, confusion, and dementia. This observation is why DD has been proposed to be relabeled as "Dercum syndrome"[80]. DD has been classified by the World Health Organization (WHO) as a distinct entity and listed as a rare disease by the Orphanet[115] and by the National Organization

for Rare Disorders (NORD)[116]. According to the latter "*Dercum Disease is a rare disorder in which there are fatty deposits which apply pressure to the nerves, resulting in weakness and pain. Various areas of the body may swell for no apparent reason. The swelling may disappear without treatment, leaving hardened tissue or pendulous skin folds*".

Steiner et al[70] referred to DD as a frequently overlooked disease and considered its assignment to the neuropathic pain syndromes to be justified. Traditional management of DD relying on weight reduction and surgical excision of particularly troublesome lesions has been largely unsatisfactory. Even at the present time, no known drug can change the course of the disease, and available treatments are only symptomatic.

Originally, Dercum[5] attributed the disease to an endocrine dysfunction, as he found atrophy of the thyroid gland. Similarly, Waldorp proposed that the disease is caused by hypophyseal dysfunction[24]. However, endocrine involvement was ruled out as early as in 1952[48]. In addition, more actual approaches have not revealed any endocrine abnormalities[12,16,59,80,117]. So, an endocrine dysfunction as the etiology of DD has little support in the modern literature.

Moreover, there are no uniform findings pointing to an inflammatory etiology in DD.

In conclusion, the findings on DD pathophysiology are still inconclusive and the clinical significance of some reports is unclear.

Based on literature data and personal experience, the perception is that this complex condition, which often takes on the contours of a real syndrome, is much more frequent than one might think. Specific research aimed at defining its pathophysiological aspects could undoubtedly allow better clinical results and therefore a strong effort by the scientific community is warranted to make the diagnosis more accurate and develop targeted therapies against such complex pathological condition which, despite being devastating for patients, is not always recognized and, too often, either underestimated or even neglected.

Conflict of interest disclosure

The authors declare no conflicts of interest.

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