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Dupuytren contracture as a sign of systemic disease

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Abstract Dupuytren contracture (DC) is predominantly an autosomal dominant disorder characterized by hypertrophy and contraction of the palmar fascia that results in tethered flexion of the affected digits. It has its highest prevalence in the North European population or in people of Viking descent, and its incidence is growing with age. DC shares a common inheritance mode, predisposing factors, comorbidities, pathophysiology, and evolution with Ledderhose disease, Garrod knuckle pads, and Peyronie disease. Nonmelanoma skin cancer also has a higher incidence in the population of North European phenotype and apparently a common genetic polymorphism. Psoriasis shares many risk factors and comorbidities with DC and has a higher prevalence in patients with DC. We suggest a close relationship among DC, some skin malignancies, and psoriasis. Regular monitoring for those skin diseases in all patients with DC is highly recommended.
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Introduction

Dupuytren contracture (DC) is predominantly an autosomal dominant disorder characterized by hypertrophy and contraction of the palmar fascia that results in tethered flexion of the affected digits.[1] The disease is well known for its associations with some metabolic, malignant, and internal diseases, but its connection to skin pathology is not well studied.

Historic perspective

The disease was described for the first time by Baron Guillaume Dupuytren (1771-1835) in 1833 as a chronic fibrotic contracture of the palmar fascia.[2] Earlier descriptions with similar characteristic can be found in the writings of Felix Plater (1536-1614) in 1614 and even earlier in the Scandinavian folklore from the 12th century.[3]

Epidemiology

DC can be found in multiple races and ethnic groups, but it has its highest prevalence in North European population or in people of Viking descent.[1,4] The disease affects approximately 4% of the population, varying greatly between geographic areas and race and rising in incidence with age. It occurs predominantly in men with a male-to-female ratio of approximately 5.9:1 and an earlier age of onset in men than in women.[5]

Etiology and pathogenesis

The way of inheritance is predominantly autosomal dominant with variable penetrance, and rarely recessive

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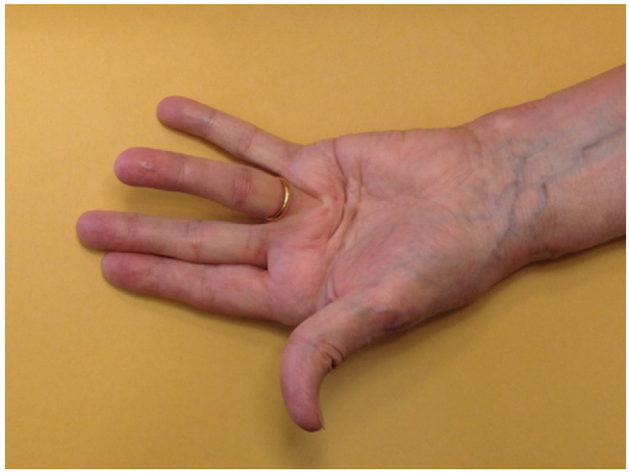

Fig. 1 Grade 1 of Dupuytren contracture presents as band in the palmar aponeurosis with skin tethering, puckering, and pitting.

autosomal or maternal. The same transmission mode is observed in the *induratio penis plastica* (Peyronie disease) and in fibromatosis of the soles (Ledderhose disease). The current pathophysiologic concept describes an early proliferation stage with formation of a nodule with increased fibrinolytic activity and transformation of the fibroblasts to myofibroblasts. It is followed by an involution stage with shrinking and compacting of the fibroblasts, and it ends with a residual stage and deposition of a large amount of extracellular type I, III, and IV collagen deposits and decreased myofibroblasts number. Various cytokines, adhesion molecules, extracellular matrix components, and growth factors, such as TGFβ1, are supposed to be involved in the proliferation and the transformation of the fibroblasts.[6]

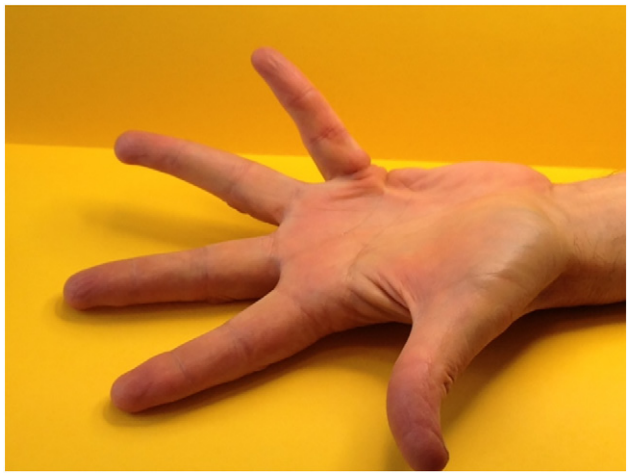

Fig. 2 Grade 2 of Dupuytren contracture presents as a peritendinous band, and limited extension of the affected finger.

Fig. 3 Grade 3 of Dupuytren contracture presents as flexion contracture of the fifth digit.

Clinical manifestations

The most frequently affected fingers are the ring finger and the little finger, but any of the fingers may be affected.[6] The first sign of the disease is the appearance of a palmar nodule, which may progress into formation of an abnormal scar-like tissue that can cause a flexion contracture. Disease progression is classified using a grading system:

- Grade 1 presents as a thickened nodule and a band in the palmar aponeurosis; this band may progress to skin tethering, puckering, or pitting (Figure 1).
- Grade 2 presents as a peritendinous band, and extension of the affected finger is limited (Figure 2).
- Grade 3 presents as a flexion contracture (Figure 3).[7]

Comorbidities and risk factors

Apart from the inheritance mode, DC shares common predisposing factors, comorbidities, pathophysiology, and evolution with Ledderhose disease, Garrod knuckle pads, and Peyronie disease. These diseases are frequently associated with DC and can be found, respectively, within 10%, 15%, and 5% of the patients with DC.[1] This is why some authors consider all of them as a part of a spectrum.

There are also several lifestyle risk factors related to an increased chance for DC.

Alcohol consumption is considered a predisposing factor, as shown in a study with 28% of alcoholic patients having DC compared with 8% of the patients in the control group.[8] The assumption that alcohol is an etiologic factor for DC is proven by several other studies, although it is not clear whether this relation is only true in alcoholic patients or whether those who drink more have a higher incidence of

the disease.[9] High prevalence of DC in patients with liver diseases is also observed, but the latter is considered to be a consequence of the increased alcohol consumption, and it is not significant in patients with nonalcoholic chronic liver disease.[10]

A high prevalence of DC is also described in heavy smokers, although it is not mentioned whether smoking is an independent risk factor or whether the patients in the study group also had increased alcohol consumption.[11]

Heavy labor and trauma are also considered important risk factors for the appearance of the disease. They were described as the main cause by Dupuytren in the first publication on the subject.[2] The association is so important that, in some studies, the DC is labeled as occupational or even an industrial disease.[12] A meta-analysis undertaken on epidemiologic studies has shown an association between high levels of work exposure and DC in certain cases.[13] Dupuytren disease has also been observed to appear after acute or specific injury, operation, or infection of the forearm, wrist, or hand, which also supports the association of an acute trauma and the appearance of the disease.[14]

Diabetes mellitus also has a high prevalence in patients with DC. It is unclear whether diabetes mellitus is a predisposing factor for DC or the pattern of inheritance predisposes to both diseases. The incidence of DC is higher in older patients with a longer history of diabetes mellitus but is usually mild and of benign prognosis, rarely needing surgical intervention.[15] The prevalence of DC seems to be the same in patients with type 1 and 2 diabetes mellitus, although it occurs at a younger age in patients with type 1 diabetes.[16]

Patients with DC have significantly more cardiovascular problems, such as hypertension and ischemic heart disease. Alcohol consumption, smoking, and diabetes mellitus have been suggested as being associated with both DC and ischemic heart disease, and so the higher prevalence of the latter in DC patients is not unexpected. Some metabolic diseases, such as higher mean serum triglyceride and cholesterol levels and gout, have also significantly higher prevalence in patients with DC.[17]

Epilepsy is also considered a frequent comorbidity for DC, with the highest incidence being 56%. DC in these patients is usually bilateral, symmetrical, and frequently associated with Garrod knuckle pads and Ledderhose disease. DC occurs equally in all forms of epilepsy and not only in the familial forms, suggesting other reasons for the association than a common inheritance pathway.[18] The prolonged use of anticonvulsants is the most reliable explanation for the incidence of DC growing with the duration of their use. A clinical regression of DC is observed after discontinuation of the treatment with phenobarbital. It is suggested that the drug has dose- and time-dependent profibrotic effect, which may be a result from stimulation of tissue growth factors.[19]

An increased prevalence of DC has been found in patients with advanced infection with HIV. DC is considered a marker of deranged free radical metabolism, which may be an intermediary mechanism in the development of AIDS and can be reduced by the use of antioxidants anti-inflammatory drugs, which explains the lower incidence of DC in patients treated with those medications for gout and rheumatoid arthritis.[9]

A recent study found an increased overall risk for cancer in patients with heavy forms of DC by 24%. Some risk factors for DC, such as tobacco and alcohol abuse, can explain to a great extent the significantly increased risks for malignancies related to smoking and increased alcohol consumption such as buccal, esophageal, gastric, lung, and pancreatic cancers and primary liver cancers.

A significantly increased risk for both prostate cancer and rectal cancer in men and an increased risk for breast cancer in women are also found. Several authors assume the existence of some characteristics in patients with DC that alter the risks for other malignancies compared with the general population.[20]

DC shares some histologic features of a neoplasm due to the marked fibroblast proliferation within the palmar nodules. It has similar infiltrative growth, proliferation, and lack of apoptosis of the mesenchymal cells, as in fibrosarcoma, and a tendency toward recurrence but without the formation of metastases. Patients with DC have increased frequency of fibrosarcoma and malignant fibrous histiocytoma that cannot be explained by common risk factors such as smoking, diabetes, or some cancer syndromes.[21]

The prevalence of different skin tumors, such as melanoma and nonmelanoma skin cancer (NMSC; basal-cell carcinoma and squamous-cell carcinoma) in patients with DC, is underestimated and not well studied. A recent retrospective study on the case notes of 181 DC patients and 41 controls has shown that DC patients had double the risk of developing NMSC compared with controls. The incidence rate of NMSC in DC patients was also higher with 17.10 new cases per 100 persons per year compared with 5.04 in the controls ($P < .05$).[22] The higher incidence of NMSC in this publication contradicts the results from previous studies.[20] The possible explanation for those results is the use of a total skin examination in the study. NMSC is a very common tumor and usually hard to find by the patient or an untrained physician. A previous study showed that only 24% of the skin malignancies are reported by patients and 55% are discovered with total skin examination.[23]

The fair "Viking skin" of the North European phenotype most common in DC patients is undoubtedly a factor that predisposes to sun-induced skin malignancy such as NMSC. DC can be regarded pathophysiologically as akin to unrestrained wound healing. This lack of cellular restraint may also render DC patients more susceptible to cancer. Another possible explanation is the existence of an xeroderma pigmentosum complementation group D polymorphism in DC patients, which is also associated with high risk of development of subsequent cancer in patients with NMSC.[24] Some premalignant skin diseases, such as solar keratosis and actinic cheilitis, have also been found to have an increased incidence in patients with DC.[25]

Psoriasis is one of the first skin diseases widely recognized for its pathogenic effects with a systemic impact. It is now considered much more a systemic disease for its close associations with various comorbidities.[26] Diseases such as type 2 diabetes, hypertension, ischemic heart disease, hypercholesterolemia, and gout are well-known comorbidities for both psoriasis and DC as well as some risk factors, such as increased alcohol consumption and smoking. Both diseases are very common and can be triggered by trauma and medications. They also have similar geographic distribution with a higher incidence in the North European population. This is why it is not surprising that a study has shown an increased prevalence of DC in patients with psoriasis compared with the general population.[27] The percentage of patients with DC is found to be 19.6% in the psoriasis population and 3.6% in the population without psoriasis. The development of DC has been shown to be more frequent in patients with predominantly palmoplantar involvement (39.1% of patients) and intertriginous psoriasis (38.9% of patients).

Conclusions

DC is a common progressive fibrotic condition affecting the palmar and digital fascia. It is considered by some authors, together with other forms of fibromatosis such as Ledderhose disease, Peyronie disease, or Garrod knuckle pads, as a part of a spectrum. They share common inheritance paths and risk factors, such as alcohol and trauma, that are frequently seen together. Most of the comorbidities of DC, such as diabetes, epilepsy, hypertension, hyperlipidemia, and gout, are well known. Other associations, such as different malignancies and AIDS, need further investigation. Some skin diseases, such as psoriasis and NMSC, appear to have a higher prevalence in patients with DC. A regular monitoring for those skin diseases in all patients with DC is highly recommended.

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