Cutaneous findings in myotonic dystrophy

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Myotonic dystrophy types 1 and 2 are a group of complex genetic disorders resulting from the expansion of (CTG)ₙ nucleotide repeats in the DMPK gene. In addition to the hallmark manifestations of myotonia and skeletal muscle atrophy, myotonic dystrophy also affects a myriad of other organs including the heart, lungs, as well as the skin. The most common cutaneous manifestations of myotonic dystrophy are early male frontal alopecia and adult-onset pilomatrixomas. Myotonic dystrophy also increases the risk of developing malignant skin diseases such as basal cell carcinoma and melanoma. To aid in the diagnosis and treatment of myotonic dystrophy related skin conditions, it is important for the dermatologist to become cognizant of the common and rare cutaneous manifestations of this genetic disorder. We performed a PubMed search using the key terms “myotonic dystrophy” AND “cutaneous” OR “skin” OR “dermatologic” AND “manifestation” OR “finding.” The resulting publications were manually reviewed for additional relevant publications, and subsequent additional searches were performed as needed, especially regarding the molecular mechanisms of pathogenesis. In this review, we aim to provide an overview of myotonic dystrophy types 1 and 2 and summarize their cutaneous manifestations as well as potential mechanisms of pathogenesis. (JAAD Int 2022;7:7-12.)

Key words: BCC; DM1; DM2; melanoma; myotonic dystrophy; pilomatrixoma; RNA toxicity; syndrome; triplet repeat expansion.

BACKGROUND

Myotonic Dystrophy type 1 (DM1) and type 2 (DM2) are autosomal dominant disorders with clinical manifestations that include myotonia, skeletal muscle atrophy, as well as multiorgan derangements such as heart conduction abnormalities, respiratory insufficiency, insulin resistance, and testicular atrophy. The prevalence of DM1, the most common type of myotonic dystrophy among adults, varies from country to country, with an estimated prevalence of 5-20 per 100,000 in European populations. Meanwhile, the prevalence in US populations has not been well-studied. It appears that DM2 is estimated to have a 5-fold lower prevalence than DM1 in the United States, though epidemiological studies are limited for DM2 as well.

Although they share many similarities, DM1 and DM2 can be distinguished by the differences in the clinical presentation, the onset of symptoms, and the absence of a congenital form of DM2 (Table I). DM1 is characterized by prominent myotonia that can be observed on clinical and electrodiagnostic examinations, whereas the phenotype for DM2 is milder. Furthermore, the weakness and muscle wasting in DM1 affect the long finger flexors, facial muscles, and dorsiflexors, whereas, in DM2, the proximal muscles such as the shoulder girdle and hip flexor muscles are commonly affected. DM2 is also frequently associated with proximal muscular pain and is commonly accompanied by a prior diagnosis of fibromyalgia.

GENETIC AND MOLECULAR MECHANISM OF PATHOGENESIS

DM1 and DM2 have similar yet distinct genetic and molecular mechanisms of pathogenesis (Table I). First identified in 1909 by Steinert et al, DM1 results from the expansion of (CTG)ₙ nucleotide repeats in the 3' untranslated region of the gene DMPK, located on chromosome 19q13.3, which encodes DMPK (myotonic dystrophy protein kinase). Asymptomatic individuals harbor between
5 and 27 CTG repeats, while individuals carrying more than 50 repeats display mild symptoms, and severe symptoms are seen in individuals carrying up to several kilobases of repeat expansions. In DM1, the length of the repeat expansion correlates with disease severity and earlier onset of disease. Furthermore, DM1 exhibits anticipation, in which the repeats expand with each subsequent generation, leading to increasing disease severity and decreasing age of onset.

In contrast, discovered less than 2 decades ago, DM2 is caused by a (CCTG)\textsubscript{n} repeat expansion in the intron of the ZNF9 gene (Table I). Normally, individuals carry less than 30 repeats, whereas DM2 patients carry between 55 and 11,000 repeats. Notably different from DM1, in DM2 the repeat expansion contracts with each subsequent generation, resulting in shorter repeats in the children, which may explain the absence of a congenital form of DM2, as well as the lack of anticipation and late-onset disease.

The fact that 2 different repeat-expansion mutations in independent genes and foci share similar clinical features points to a common mechanism of pathogenesis. Like other repeat-expansion disorders such as Fragile X-associated tremor/ataxia syndrome, the pathogenesis of DM1 and DM2 is thought to result mainly from gain-of-function RNA toxicity, in which mutant RNAs harboring the expanded repeats accumulate in the cell nuclei forming ribonuclear inclusions and lead to sequestration of RNA binding proteins such as CUG-binding protein 1 and muscleblind-like protein 1, perturbing their usual function. Taneja et al. have demonstrated the accumulation of nuclear transcripts containing CUG repeat expansion in both cultured fibroblasts and skeletal muscle biopsies from DM patients. Furthermore, seminal work by Timchenko and colleagues over several decades led to the discovery of the first of the sequestered RNA binding proteins, CUG-binding proteins, which sequester to the CUG trinucleotide repeat in the \textit{DMPK} pre-mRNA and affect the processing and turnover of the \textit{DMPK} mRNA.

In addition to RNA toxicity, repeat associated non-ATG translation (RAN translation) of the CAG repeats is another mechanism that has been shown to contribute to the pathogenesis of DM1 through the accumulation of polyglutamine expansion proteins in mouse models of DM1 as well as human tissue. RAN translation has also been demonstrated in DM2, through the expression of tetrapeptide poly-(LPAC) and poly-(QAGR) RAN proteins in the brains of DM2 patients, not controls. LPAC RAN proteins were demonstrated to be present in neurons, astrocytes, and glia in the gray matter of DM2 autopsy brains, while antisense QAGR proteins accumulated within the white matter of DM2 patients.

In vivo, mouse models of DM1 have demonstrated that the CTG repeats lead to skeletal muscle weakness and myotonia. Mankodi et al. were the first to demonstrate that the expression of CUG transcripts is sufficient to generate the DM phenotype in mice, supporting RNA-gain-of-function as playing a crucial role in disease pathogenesis. Despite herculean efforts in the field, much still remains to be known regarding the mechanistic role of the mutant CTG repeats and the associated contributions of RNA toxicity, RAN translation, and other mechanisms in the molecular pathogenesis of DM1. In particular, studies have been limited on the molecular pathogenesis of DM2 and necessitates further research.

**CAPSULE SUMMARY**

- Though generally regarded as a musculoskeletal disorder, myotonic dystrophy affects multiple organs including the skin, and confers increased risk for developing benign and malignant cutaneous disease.
- This article summarizes the cutaneous manifestations of myotonic dystrophy and provides an update on the current understanding of the mechanisms of pathogenesis.

**BENIGN CUTANEOUS MANIFESTATIONS**

The most frequent cutaneous features in DM1 are early male frontal alopecia and the development of pilomatricomas that manifest as small firm papules/nodules that are frequently calcified (Table II). Multiple pilomatricomas are rare and have been associated with a number of syndromes including myotonic dystrophy, familial adenomatous polyposis-related syndrome (including Gardner syndrome), Turner syndrome, and Rubinstein-Taybi syndrome. The association between DM and pilomatricomas was first described in 1965 and has been followed by numerous case reports. A review in 2011 identified 35 published cases to date on the association between DM and pilomatricoma, 89% of which described myotonic dystrophy patients with multiple pilomatricomas. In contrast to nonsyndromic pilomatricomas, DM-associated pilomatricomas commonly manifest in adulthood and often originate in the scalp. Interestingly, in DM1, pilomatricomas can also develop as isolated lesions in childhood and may serve to herald the first sign of
disease. In fact, a recent article has alerted pediatric dermatologists to investigate for an underlying syndrome if a patient presents with greater than 6 pilomatricomas or presents with less than 6 pilomatricomas and relevant family history such as the family history of myotonic dystrophy.

Nonsyndromic pilomatricomas are known to be caused by somatic mutations in CTNNB1, the gene that encodes β-catenin, an intracellular protein that functions as a downstream effector of the Wnt signaling pathway, and also plays a role in intercellular adhesion. In nonsyndromic pilomatricomas, the somatic mutation results in a mutant β-catenin that is resistant to ubiquitination and phosphorylation and accumulates in the nucleus and cytoplasm of the matrix (basaloid) cells. The increased levels of β-catenin lead to the activation of transcription, increased Wnt signaling, increased apoptosis, and abnormal proliferation, resulting in pilomatricoma. It has been proposed that the increased susceptibility to pilomatricomas in muscular dystrophy patients may also occur via dysregulation of the Wnt/β-catenin signaling pathway. Alternative hypotheses suggest that the accumulation of untranslated repeat RNA in the cell nucleus may result in either direct or indirect interference of DNA proofreading or replication.

Recently, Rubben et al. investigated the molecular mechanisms behind the development of multiple pilomatricomas and cancer in patients with DM1 by sequencing CTNNB1 in 5 samples; 4 pilomatricomas and 1 pilametary carcinoma that developed in 1 patient with molecularly diagnosed DM1. They identified multiple different somatic mutations that are not shared between the 5 samples and hypothesized that the simultaneous transcription of the mutated DMPK and CTNNB1 genes in the cycling hair follicles may result in tissue and gene-specific hypermutability of DM1 patients. Given the small sample size of this study, it would be most valuable to conduct a larger-scale study in order to validate the hypermutability hypothesis and to screen for any driver mutations in CTNNB1 that may contribute to the development of pilomatricomas in DM1 patients.

Furthermore, DM1 and DM2 have also been associated with clinical nevi abnormalities and signs of premature aging, with a higher frequency of dysplastic nevi, xerosis, alopecia, and seborrheic dermatitis (Table II). Interestingly, in DM1, the number of nevi was demonstrated to correlate with the size of the CTG expansion. Furthermore, in addition to pilomatricomas and dysplastic nevi, other benign neoplasms have been associated with DM as well. One case report described a 63-year-old woman with DM1 presenting with multiple heman-giomas of the tongue and oral cavity.

**SKIN CANCER AND MYOTONIC DYSTROPHY**

In addition to its association with benign cutaneous neoplasms, myotonic dystrophy has also been linked to malignant skin cancers, especially basal cell carcinoma (BCC) (Table II). In 1986, dermatologists in Germany first reported the association between myotonic muscular dystrophy and BCC. Since then, 9 case reports have been published on DM1 patients presenting with multiple BCC suggesting an association between the repeat-expansion disorder and BCC. A UK retrospective study on 1061 DM1 patients and 15,119 DM1-free matched individuals in the UK Clinical Practice Research Datalink demonstrated an increased risk of all skin cancers in DM1 patients compared to their matched DM1-free controls, with the highest risk for BCC (hazard ratio, 5.78; 95% CI, 3.36-9.92; \( P < .0001 \)). DM1 patients also demonstrated an approximately 2-fold increase in melanoma risk, though not statistically significant. Interestingly, there were no reports of squamous cell carcinoma incidence in these DM1 patients. A smaller study conducted in Spain of 102 Caucasian patients demonstrated that the mean age at diagnosis was significantly lower among patients with DM1 compared to controls, which further substantiates the argument that DM1 may predispose patients to the development of BCC.

Although most data on skin cancers associated with DM are limited to BCC, a meta-analysis of 5 cohort studies (2 clinic-based and 3 population-based) of 2779 patients in multiple countries (Sweden, Denmark, France, Spain, US) affirmed that patients with myotonic dystrophy are at increased risk of cutaneous melanoma (\( P = .005 \)). Notably, this meta-analysis included patients with both DM1 and DM2. Furthermore, a study of 927 DM1 patients and 13,085 DM1-free individuals in the UK Clinical Practice Research Datalink demonstrated that classic DM1 patients are at an increased risk of cancer overall, including cancers of the thyroid, uterus, and cutaneous melanoma. They went on
to show that DM1-related cancer susceptibility is modulated by the severity of myotonic dystrophy. Studies have been conducted to ascertain whether the association between DM1 and tumor development is based on biological predisposition rather than external environmental factors. In a 2016 study conducted on 255 patients in 1 of 4 main hospitals for DM patients in Rome, Italy, the authors diagnosed 59 benign tumors in 54 patients and 19 malignant tumors in 17 patients. They found an increased risk of malignant tumors including skin cancer in DM1 patients compared to age-matched controls, but failed to find any association of tumor development with exposure to common lifestyle risk factors such as alcohol consumption, smoking, obesity, or co-morbidities such as diabetes. Similar results were reported in 2017, in a study on 220 patients enrolled in the UK Myotonic Dystrophy Patient Registry. These findings reaffirm that the observation of increased cancer risk in DM1 patients must be primarily driven by genetics rather than environmental influences. Further research is warranted to elucidate the molecular mechanism of tumorigenesis in DM1 in order to aid in providing treatments and prognoses for these patients.

**ROLE OF DMPK1 IN TUMORIGENESIS VS TUMOR SUPPRESSION**

Our understanding of the role of DMPK1 in tumor development is still in its infancy. Using a novel pyrazol-urea kinase inhibitor, GeGe3, Meta et al have identified DMPK1 as a novel mediator of angiogenesis. Using confocal microscopy, they reported that DMPK1 is present in the nucleus and cytoplasm of endothelial cells. They also showed that DMPK1 plays a role in the activation of MAPK signaling, as well as endothelial cell proliferation and migration. GeGe3 was demonstrated to be an effective inhibitor of tumor angiogenesis by targeting DMPK1 activity and protein level. This finding not only lends fuel for further development of novel antiangiogenic drugs based on the GeGe-3 structure but also provides a potent inhibitor as a tool to study DMPK's role in the genesis of BCC and cutaneous melanoma in myotonic dystrophy.

In contrast, in a recent study, Itoh et al demonstrated that DMPK is a novel candidate mediator of tumor suppressor p53-dependent apoptosis. The authors suggest the existence of a p53-p73-DMPK axis that modulates DNA-damage induced actomyosin contraction leading to apoptosis. Their data shows evidence to support the hypothesis that in response to DNA damage, p53 induces the expression of DMPK through the upregulation of p73 expression. Taken together, these recent findings point toward two critical potential roles of DMPK in cell death as well as tumor angiogenesis. Further research is warranted to better understand this potential dualistic role of DMPK.

**FUTURE DIRECTIONS**

In summary, DM1 and DM2 are genetic repeat-expansion disorders that should become more familiar to dermatologists given their cutaneous manifestations (Table II). Pediatric dermatologists may be the first specialist to examine patients with

**Table I. Brief comparison of DM1 and DM2**

<table>
<thead>
<tr>
<th>Disease characteristic</th>
<th>DM1</th>
<th>DM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>CTG repeat expansion in 3’UTR of DMPK</td>
<td>CCTG repeat expansion in an intron of ZNF9</td>
</tr>
<tr>
<td></td>
<td>Repeat expansion with each subsequent generation</td>
<td>Repeat contraction with each subsequent generation</td>
</tr>
<tr>
<td>Onset</td>
<td>0-adult</td>
<td>8-60 years</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Prominent myotonia</td>
<td>Mild myotonia</td>
</tr>
<tr>
<td></td>
<td>Weakness and muscle wasting in long finger flexors, facial muscles, and dorsiflexors</td>
<td>Weakness in proximal muscles (shoulder girdle, hip flexors muscles)</td>
</tr>
<tr>
<td>Congenital form</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

DM1, Myotonic dystrophy type 1; DM2, myotonic dystrophy type 2.

**Table II. Benign and malignant cutaneous manifestations of DM1 and DM2**

<table>
<thead>
<tr>
<th>Neoplasm category</th>
<th>DM1 only</th>
<th>DM1 and DM2</th>
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<tbody>
<tr>
<td>Benign</td>
<td>Early male frontal alopecia</td>
<td>Nevi abnormalities</td>
</tr>
<tr>
<td></td>
<td>Pilomatricomas</td>
<td></td>
</tr>
<tr>
<td>Other benign neoplasms (eg, multiple hemangiomas of tongue and oral cavity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Basal cell carcinoma</td>
<td>Cutaneous melanoma</td>
</tr>
</tbody>
</table>

DM1, Myotonic dystrophy type 1; DM2, myotonic dystrophy type 2.
childhood-onset disease, and adult patients can present to dermatologists with various cutaneous manifestations including multiple pilomatrixomas, alopecia, and BCC.

Much remains unknown regarding the molecular mechanisms behind DM1 and DM2, and especially regarding the pathogenesis of the benign and malignant cutaneous manifestations. Although the association between myotonic dystrophy and BCC was reported more than 3 decades ago, it is only within the last few years that studies have endeavored to further investigate whether this association holds true. Recent studies across Europe and the US have demonstrated that myotonic dystrophy is strongly associated with BCC as well as cutaneous melanoma. Our next task over the following decade is to fill the gap in our understanding of the molecular mechanisms behind this association for the development of future therapeutics and the identification of biomarkers for diagnostic and prognostic purposes.

Given that DMPK may be a key player in tumorigenesis and programmed cell death, future studies in DM1 should focus on determining whether the mutant DMPK RNA affects the cell’s ability to carry out apoptosis. Further, it would be valuable to investigate whether the mutant DMPK RNA affects tumor angiogenesis.

For future clinical studies, it would be important to first validate the report by Alsaggaf et al.14 that DM1 disease severity modulates DM1-associated cancer susceptibility in cutaneous DM1-related cancers, such as BCC and melanoma. Furthermore, as mentioned previously, it would be essential to build on the clinical studies so far by expanding basic science research on elucidating the mechanisms of pathogenesis of DM-associated BCC and melanoma, which will serve to facilitate the development of therapeutic drugs.

**Conflicts of interest**

None disclosed.

**REFERENCES**


