Case report

Myotonic dystrophy and recurrent pleomorphic adenomas: Case report and association hypothesis

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Abstract

We report a case of a patient with concurrent myotonic dystrophy and recurrent pleomorphic adenoma and hypothesize the association between both diseases. A 58-year-old man with classic myotonic dystrophy type 1 was diagnosed with pleomorphic adenoma. Appropriate treatment was commenced. Massive recurrences occurred within 15, 28 and 22 months respectively, after repeated surgical removal. Three case reports on similar occurrences of synchronous myotonic dystrophy and pleomorphic adenoma are discussed and an association between both disease entities is hypothesized. A conceivable association between myotonic dystrophy and pleomorphic adenoma is hypothesized by upregulation of the Wnt/Beta-catenin signaling pathway, initiated by a decreased expression of microRNA, pleomorphic adenoma gene 1 induced Beta-catenin accumulations and alterations in tumor suppressor genes and oncogenes due to RNA processing defects induced by the expanded repeat in the DMPK gene.

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1. Background

Myotonic Dystrophy type 1 (DM1) is a rare autosomal dominant disease with an estimated prevalence of 1:8.000. DM1, formerly known as Steinert disease, is one of the two major forms of Dystrophia Myotonica (DM), resulting from an unstable Cytosine-Thymine-Guanine (CTG) trinucleotide repeat expansion in the 3′-untranslated region of the Dystrophia Myotonica Protein Kinase (DMPK) gene, on chromosome 19q 13.3. Generally, longer CTG repeat expansions correlate with an earlier age at onset and more severe disease [1]. The repeat expansion is however mitotically unstable in individuals with DM1, leading to somatic mosaicism in the CTG repeat length between various tissues and organs, partially explaining the wide phenotypic variability. The effect of the expanded CTG repeat remains complex, although it is thought this mainly occurs through abnormal RNA transcript processing in antagonistic proteins of splicing events disrupted in patients with DM1 [2–4]. Other additional factors contributing to DM1 are still being studied and remain unknown. The disease is mainly characterized by muscle weakness and myotonia but affects other organ systems as well, causing early onset cataract, cardiac conduction disturbances, respiratory insufficiency, insulin resistance and infertility. Patients with DM1 have an increased risk of developing benign and malignant tumors. The most commonly associated and described neoplasm being the pilomatrixoma, which is a rare benign calcifying cutaneous tumor [5]. They are however also at an increased
risk for endometrium, brain, ovary, colon, testicular and thyroid tumors, choroidal melanoma and possible prostate cancer [5–8]. Additionally it was recently described that, in comparison to 13,085 matched DM1-free individuals, salivary gland adenomas occurred at a relatively high frequency in 927 DM1 patients [9].

Salivary gland tumors, however, are rare, accounting for approximately 3 cases per 100,000 inhabitants every year [10]. Most salivary gland tumors arise in the parotid gland, of which 75% is benign and 25% malignant [10]. Pleomorphic adenoma is the most common benign salivary gland tumor and usually presents as a slowly growing painless swelling. However, pleomorphic adenomas may undergo malignant transformation even after many years. The risk for malignant transformation increases up to 10% after 15 years. Therefore, pleomorphic adenomas are surgically removed.

Recurrences of pleomorphic adenomas are a challenging problem and occur in approximately 2% of patients after a superficial parotidectomy, usually after 7–10 years. A total parotidectomy reduces the recurrence rate to 0.4% [11–13]. The likelihood of recurrence is higher in relatively young patients, when resection margins are positive and when the tumor capsule was ruptured during surgery [12,14]. Surgical removal of a recurrence with as much normal surrounding gland tissue as possible, with or without postoperative radiotherapy, consecutively reduces the probability of recurrences significantly [12,15].

In addition to three case reports describing the occurrence of pleomorphic adenoma in DM1 patients [16–18], here we report a patient with DM1 and multiple reoccurring pleomorphic adenomas and highlight a hypothesis that associates both diseases.

2. Case report

A 58-year-old man was referred to the Ear, Nose, and Throat (ENT) department in November 2011 by his general practitioner with an increasing painless swelling in the right parotid region since 5 months. The patient was known to have classic DM1 since 1991 (repeat size unknown) based on clinical features and family history as his mother and brother were diagnosed with DNA confirmed DM1. The DM1 was characterized by a mild muscle weakness in the distal arms and legs, a typical myopathic face and a reduced processing speed. The history of the patient mentioned an ileus in 2003 which was surgically treated, proctitis, gout and obstructive sleep apnea. There was no family history of cancer. The patient did not smoke or drink alcohol. ENT examination revealed a swelling in the right parotid region with indefinable boundaries. No other abnormalities were found. Magnetic Resonance Imaging (MRI) illustrated a large space occupying lesion in the deep parapharyngeal right parotid lobe without invasion of surrounding tissues (Fig. 1). Fine needle aspiration (FNA) of the lesion, showed a pleomorphic adenoma without malignant features. An external deep parotid dissection was performed in January 2012; no complications, i.e. facial nerve damage, occurred. Histology showed a radically removed, entirely encapsulated pleomorphic adenoma of 30 mm.

In April 2013, 15 months after initial surgery, the patient detected a painful swelling in the right submandibular region. An ultrasound showed two submandibular lesions of 11 mm and 16 mm. Multiple cystic structures suspect for recurrent pleomorphic adenomas in the right prestyloid parapharyngeal space, reaching until the right submandibular region were seen on MRI (Fig. 2). FNA of the two submandibular lesions

Fig. 1. T2-weighted Magnetic Resonance Image (MRI) (December 2011) of a large pleomorphic adenoma in the right deep parotid lobe indicated with the white arrow in the coronal (a) and axial (b) planes.
was suspicious for a pleomorphic adenoma. Therefore in June 2013, a right re-parotidectomy was performed in which multiple histological confirmed pleomorphic adenomas were resected. The facial nerve could again be preserved. Due to some remaining lesions which were impossible to resect, the patient received additional postoperative radiation therapy and was closely followed up.

Throughout the follow-up period multiple MRI’s showed stable disease until October 2015, when the patient developed renewed pain in the right parotid region. Meanwhile he felt that he could not close his right eye properly and that the right side of his mouth drooped, suggesting facial nerve involvement. However, on physical examination a facial nerve palsy was hard to assess, due to the DM1. MRI showed an increase of the lesions in the right parapharyngeal space and new lesions in the deep right parotid lobe. Therefore, in December 2015, a deep right lobe parotidectomy in combination with a mandibular split and temporary tracheotomy was performed to remove all lesions, sacrificing the right facial and lingual nerve. Histological analysis showed re-recurrence of the pleomorphic adenomas without any malignant degeneration. Additional radiation therapy was not feasible this time, because of the patients’ post-surgical weakened physical state.

By the end of October 2017, 22 months after the last surgery, a small right pre-auricular painful swelling and two small swellings in the previous scar had appeared. An MRI to determine the extent of the swellings showed a severely extended tumor, suspicious of pleomorphic adenoma, in mainly the right parotid region and right parapharyngeal space of $88 \times 37\text{mm}$ (Fig. 3). The tumor extended into the stylohyoid and foramen ovale and mandibular foramen and caused vigorously mediatisation of the nasopharynx and cranial tonsil loge. Thus even though all pleomorphic adenomas appeared to be surgically removed in December 2015, 22 months later a third massive recurrence, within 4.5 years after primary surgery, was confirmed by FNA. Several days after the MRI, the patient suddenly died due to aspiration.

3. Discussion

Despite adequate multiple resections and postoperative radiation therapy after the first recurrence, our patient experienced two rerecurrences. While multiple recurrences of pleomorphic adenoma have been reported, recurrence within 15 months after initial radical surgical removal, and recurrence within 28 and 22 months respectively after repeated extended surgery and additional radiation therapy is rare [11]. This unusual progressive and aggressive recurrence behavior and short time period between recurrences and re-recurrences, raised the suspicion of an association with the coexisting DM1. An extended literature search in PubMed with the terms ‘myotonic dystrophy’ OR ‘Steinert’ AND ‘pleomorphic adenoma’ resulted in three additional cases.

Johannesson [16] was the first to report the coexistence of myotonic dystrophy and pleomorphic adenoma in two women in 1978, statistically arguing that the probability of coincidence due to chance was too small, suggesting there had to be factors predisposing to parotid neoplasms in myotonic dystrophy. In 1998 Ogata et al. [17] suggested that the extension of CTG repeats was related to active cell division and to the occurrence of tumors in patients with myotonic dystrophy. They used a Southern blot analysis showing that the CTG repeat in the pleomorphic adenoma tumor DNA of a 60-year-old patient was more expanded than in the other parotid gland. Insights in the causative role of somatic mosaicism, the presence of a genetically distinct cell population within an organism [19], has previously been described in cancer and many non-tumorous neurodegenerative and complex diseases [20–24]. Draper and Pickles [18] described another two cases of patients with myotonic dystrophy and pleomorphic adenoma in 2000, of which one concerned a 9-year-old girl. They proposed that the occurrence of pleomorphic adenoma at such a young age in a girl with congenital myotonic dystrophy was so rare, that an association between the two disease entities was highly likely.

Additional literature research learned that pilomatrixoma, a benign calcifying cutaneous tumor, which is the most common neoplasm in patients with DM1 [5], contains somatic mutations in the gene encoding for β-catenin (CTNNB1), resulting in an accumulation of β-catenin [25]. As component of the Wnt/β-catenin signaling pathway, which is crucial in
human organ development and involved in tumor progression of many cancers, an accumulation of β-catenin up regulates the Wnt/β-catenin signaling pathway.

Accumulations of β-catenin have also been shown in CTNNB1-mutated thyroid carcinoma, one of the other cancers frequently seen in patients with DM1 [5,8]. Many tumors however accumulate β-catenin in the absence of mutations in CTNNB1, suggesting other sources leading to β-catenin accumulations [26].

In pleomorphic adenomas, the pleomorphic adenoma gene 1 (PLAG1) seems to play a crucial role in tumorigenesis and β-catenin accumulation. Zhao et al. [27] used transgenic mice to demonstrate that overexpression of PLAG1 induces upregulation of β-catenin and thereby the Wnt/β-catenin signaling pathway, leading to the development of pleomorphic adenomas in the parotid glands of mice.

The exact pathogenetic and molecular carcinogenesis mechanisms in DM1 remain undefined. The most appealing hypothesis yet is the alteration of oncogenes or tumor suppressor genes due to RNA processing defects induced by the expanded repeat in the DMPK gene, increasing the risk of neoplasm development. Fernández-Torrón et al. observed a decrease in the expression of the microRNA-200/microRNA-141 tumor suppressor family in women with DM1 in comparison to a control of healthy people [28]. Recent evidence shows that microRNA-200 is a key modulator in the Wnt-signaling pathway and capable of directly interacting with CTNNB1 (the gene encoding β-catenin) to suppress Wnt/β-catenin signaling [29,30]. A decreased expression of this microRNA might thus lead to tumor formation and the occurrence of pleomorphic adenoma in patients with DM1. Future studies investigating the exact pathogenic mechanisms underlying pleomorphic adenomas and tumor behavior in patients with DM1 are needed to establish targeted therapeutic interventions and guide clinical management and follow-up.

Currently, clinicians treating patients with DM1 are advised by the consensus-based care recommendations to train patients in detecting small hard lumps under the skin, near the hairline and on the neck, suspicious for pilomatrixomas [31]. We advise them however to also be aware of lumps in the parotid area suspicious for pleomorphic
adenoma and advise them to refer these patients for evaluation and clinical work-up as pleomorphic adenoma usually need surgical treatment to prevent malignant transformation.

4. Conclusion

Patients with DM1 are known to have an increased risk of benign and malignant tumors of the endometrium, brain, ovary, colon, testis, thyroid, possibly the prostate as well as an increased risk of choroidal melanoma. In addition our case highlights a possible association between DM1 and reoccurring pleomorphic adenomas. While the exact underlying pathologic mechanism in the pathogenesis for DM1 and concurrent neoplasms remains unclear, the hypothesis of an unsuppressed Wnt/β-catenin signaling pathway via decreased expression of micro-RNA and up regulation of β-catenin by PLAG1, in combination with the alteration of tumor suppressor genes and oncogenes due to RNA processing defects induced by the expanded repeat in DMPK might lead to the formation of myotonic dystrophy associated pleomorphic adenomas. In this light we advise clinicians treating patients with DM1 to be aware of, and evaluate lumps in the parotid region as these may be pleomorphic adenomas in need for surgical treatment.

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