Chapter 2

Xerostomia

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Summary

Xerostomia is the subjective feeling of oral dryness. Several diseases and conditions have been associated with xerostomia. Three major causes are: Sjögren’s syndrome, medication and radiotherapy in the head and neck.

Sjögren’s syndrome is a chronic systemic autoimmune disease characterised by infiltration of the exocrine glands, the salivary and lacrimal in particular. The pathogenesis involves systemic B-cell hyperactivity and T-cell lymphocytes targeting glandular epithelial cells. About 75% of patients with Sjögren’s syndrome develop malignant B cell lymphoma, mostly mucosa associated tissue lymphomas (MALT).

Certain classes of drugs can induce hyposalivation and/or xerostomia by, e.g., targeting neurotransmitters and receptors. As a result, amongst others the production of fluid and electrolytes in salivary glands can be reduced and the salivary composition can change.

During head and neck radiotherapy, the administration of high doses to the major salivary glands, which are located in the periphery of the head, leads to progressive loss of glandular function and a diminished salivary output. In particular, reduction of the dose to and the volume of irradiated salivary glands by advanced radiotherapy techniques can be highly beneficial for patients.

Introduction

Xerostomia is the subjective feeling of oral dryness. The term is derived from the Greek words “xéros” (ξηρός), meaning dry and “stoma” (στόμα), meaning mouth. The prevalence of xerostomia is difficult to be determined and numerous studies estimate it between 13 and 63% [1]. It is more prominent in women, in elderly and in individuals housed in long-term care facilities. A number of factors may cause or has been associated with transient or persistent xerostomia (Table 1). This chapter will focus on the three most common causes: Sjögren’s syndrome, medication and radiotherapy of the head and neck.

Sjögren’s syndrome

Sjögren’s syndrome (SS), in the form that it is currently defined, was first described by the Swedish ophthalmologist Henrik Sjögren in 1930. It is a chronic inflammatory and lymphoproliferative disorder that is principally characterised by chronic infiltration of the exocrine glands. It commonly affects the salivary and lacrimal glands, resulting in xerostomia and dry eyes (keratoconjunctivitis sicca). These symptoms, known also as sicca symptoms, may be accompanied by extraglandular manifestations, evident in almost any organ. According to the American-European Consensus Group (AECG) classification criteria [2], SS can be distinguished in primary Sjögren’s syndrome (pSS), in case no other autoimmune disease is present, and secondary Sjögren’s syndrome (sSS), in case additional connective tissue diseases are present, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma and mixed connective tissue disease.

Epidemiology

SS is one of the most common rheumatic diseases, with a prevalence of 0.5-1% in the total population. It affects mainly women (i.e. female to male ratio equals to 9:1). The median age of occurrence is around 50 years, although it can arise in all ages. In RA the prevalence of SS is around 30% and approximately 20% of patients with SLE fulfil the criteria for sSS.

Clinical features

Glandular manifestations

SS primarily affects lacrimal and salivary glands. With respect to the eyes’ symptoms, dryness may result in sensation of itching, grittiness, and soreness, notwithstanding the eyes’ appearance can be normal. Ocular complaints may include...
Table 1: Conditions causing xerostomia (modified after Jensen et al., 2010).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Changed composition</th>
<th>Changed composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerogenic drugs</td>
<td>+</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td>+</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Head &amp; neck radiotherapy</td>
<td>+</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>Chronic inflammatory connective tissue diseases</td>
<td></td>
<td>Metabolic disturbances</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>?</td>
<td>Water and salt imbalance</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>?</td>
<td>Sodium retention syndrome</td>
</tr>
<tr>
<td>Chronic inflammatory bowel diseases</td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Autoimmune liver diseases</td>
<td>?</td>
<td>Eating disorders</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td></td>
<td>Bulimia nervosa</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td></td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>?</td>
<td>Cancer-associated disturbances</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>?</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td>GVHD</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Neurological disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Holmes-Adie syndrome</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Burning mouth syndrome</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Enlargement of the salivary glands, especially the parotid and submandibular glands (Figure 4) is a common phenomenon in patients with SS. Swelling of the salivary glands is usually bilateral, may be non-painful to slightly tender and intermittent to persistence in nature. The swelling is generally attributed to the presence of an autoimmune inflammatory process in these glands and stasis of saliva can result in secondary infection, encouraging further swelling. The development of lymphomas, in most cases in the parotid gland, can lead also to more persistent unilateral glandular enlargement. Dryness can occur at mucosal surfaces of upper and lower respiratory tracts resulting in non-productive cough [5]. Dry skin affects about 55% of SS patients while in female patients with SS desiccation of the vagina results in dyspareunia [6].

Another prominent symptom of SS is xerostomia (sensation of dry mouth related to a reduced saliva production). This symptom is often associated with dysgeusia, difficulty in eating dry food (e.g. crackers), problems in speaking for long period of time, burning sensation of the mouth, discomfort while wearing dentures, and increased risk of dental caries, especially cervically (Figure 2), and oral infection, in particular candidiasis. In the onset of SS, mouth appears to be normally moisturised but while the disease progresses, saliva diminishes and becomes foamy, lacking of the usual pooling in the floor of the mouth. In advanced disease, the oral mucosa is tender and dry and characteristically forms fine wrinkles (Figure 3). The tongue, in particular, often becomes fissured and exhibits atrophy of the papillae.
Chapter 2

Lymphoma development
About 7.5% of patients with SS develop malignant B cell lymphoma, 48-75% of which is MALT-type [7,8]. SS patients also have an 18.8 (CI: 9.5-37.3) times increased risk in developing lymphomas [9]. B cell lymphomas are most frequently located in the parotid gland. The conversion from variable to persistent enlargement of the gland is an alarming clinical sign. The presence of palpable purpura (Figure 5), vasculitis (Figure 6), renal involvement and peripheral neuropathy, although not pathognomonic, should raise suspicion, especially when it is combined with monoclonal gammopathy, reduced levels of complement C4, CD4+ T lymphocytopenia, sharp increase in IgG levels, or cryoglobulinemia [7-12] (Table 2).

Serological findings
The most characteristic autoantibodies in SS are the anti-Ro/SSA and anti-La/SSB autoantibodies (Table 3), which are present in 70% and 50% of cases, respectively. Their titers reflect disease activity, while high titers of particularly anti-La/SSB have been associated with extraglandular disease [13]. Despite anti-Ro/SSA and anti-La/SSB are not specific for SS, since they can also occur in, e.g., patients with SLE, their presence should alert the clinician for the possibility of SS-diagnosis.

Diagnostic criteria
A joint study of the AECG presented in 2002 the revised AECG classification criteria for SS and since to date they are the most widely accepted criteria [2]. These criteria successfully combine subjective symptoms, as well as objective signs of keratoconjunctivitis sicca and hyposalivation together with histopathological and serological findings. It must be underlined that SS can be present in a patient who does not completely fulfill these classification criteria and that since anticholinergic drugs are widely used by patients for many conditions, their exclusion should be carefully re-evaluated [1]. Recently, due to the emergence of biologic agents, the American College of Rheumatology (ACR) proposed new classification criteria for SS, based merely on objective tests. The ACR classification criteria were developed from registry data collected with standardized measures and are thought to be more suitable in situations where misclassification may present health risks [14].

Etiopathogenesis
SS is considered to be an autoimmune disorder, but with a pathogenesis that is poorly understood. Undoubtedly, a disturbance of the immune system plays a key role. It is not clarified yet whether this disturbance exists primarily or is a result of an infection, possibly viral or has another cause. Several findings suggest that viruses, such as Epstein Barr, Coxsackie and retroviruses may be implicated. Possibly, their glandular persistence in salivary gland epithelial cells may lead to chronic lymphocytic sialoadenitis with formation of foci around the ducts [15]. Additionally, hepatitis C and HIV infections can produce both symptoms and pathological find-

Table 2: Risk factors for the development of lymphoma.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Serological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent enlargement of parotid gland</td>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td>Persistent lymphadenopathy</td>
<td>Reduced levels of complement C4</td>
</tr>
<tr>
<td>Palpable purpura</td>
<td>CD4+ T lymphocytopenia</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Increase in IgG levels</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Serologic findings in SS patients.

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Frequency in SS patients (%)</th>
<th>Specific for SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Ro/SSA</td>
<td>70</td>
<td>NO</td>
</tr>
<tr>
<td>anti-La/SSB</td>
<td>50</td>
<td>NO</td>
</tr>
<tr>
<td>anti-alpha fodrin</td>
<td>30</td>
<td>YES</td>
</tr>
<tr>
<td>anti-muscarinic acetylcholine receptor 3</td>
<td>71-90</td>
<td>NO</td>
</tr>
<tr>
<td>rheumatoid factor</td>
<td>50</td>
<td>NO</td>
</tr>
</tbody>
</table>

Table 4: Possible factors predisposing to SS.

<table>
<thead>
<tr>
<th>Endogenous</th>
<th>Exogenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic disturbance</td>
<td>Virus infection</td>
</tr>
<tr>
<td>HLA-DR3/DQ-2</td>
<td>1. Epstein Barr</td>
</tr>
<tr>
<td>Female gender</td>
<td>2. Coxsackie</td>
</tr>
<tr>
<td></td>
<td>3. Retroviruses (e.g., HTLV-10)</td>
</tr>
<tr>
<td></td>
<td>4. HIV</td>
</tr>
<tr>
<td></td>
<td>5. Hepatitis C</td>
</tr>
</tbody>
</table>
The procedure is performed under local anaesthesia. A lower lip mucosa incision of approximately 1.5 cm is made and at least seven individual labial glands are collected [19]. Parotid biopsies are increasingly gaining broader acceptance and are used as an alternative to minor salivary gland biopsies. Parotid biopsies are validated for the AECG classification criteria [20], but not yet for the ACR classification criteria. With this technique, also performed under local anaesthesia, parotid tissue is taken from the area around the lower ear lobe. An 1 cm incision is carried out, followed by blunt dissection to the parotid gland and an incisional biopsy. The remaining wound is closed in layers [21] (Figure 7). Several studies show a lower morbidity of a parotid gland biopsy compared to a lip biopsy [20,22] with regard to loss of sensibility and pain. In none of the parotid gland biopsy studies a disturbance of the facial nerve was observed.

Figure 5: Purpura is a common extraglandular manifestation in SS patients.

The complexity of the pathogenetic pathways in SS involves both systemic B-cell hyperactivity and also T-cell lymphocytes targeting glandular epithelial cells:

- Prolonged B-cell survival and B-cell hyperactivity leads to presence of anti-Ro/SSA and anti-La/SSB antibodies, RF, type 2 cryoglobulins and hypergamma-globulinemia in SS patients;
- Ductal epithelial cells are surrounded by activated T-cells, predominantly CD4-positive (70-80%). CD8-positive T-cells constitute around 10% of infiltrating cells in affected labial salivary glands [18].

Histopathology
Biopsy of the minor salivary glands of the lower lip is widely used for the diagnosis of SS and its histopathology is considered as one of the four objective AECG classification criteria of SS as well as one of the three objective ACR criteria [2,4].
The most prominent microscopic finding in SS is periductal lymphocytic infiltration of salivary glands in combination with destruction of acini (Figure 8A). The infiltrates are composed of both B- and T-lymphocytes as well as non-lymphoid cells and are located around the striated ducts. When these infiltrates are composed of more than 50 cells, they are called focus. The presence of more than one focus per 4 mm² area of glandular tissue is regarded as a positive criterion for the diagnosis of SS. Furthermore, if the major glands are enlarged, progression to a lymphoepithelial lesion (LEL) (Figure 8B) can also be present. In major salivary glands, characteristic epimyoepithelial islands in a background of lymphoid stroma are usually seen.

The sensitivity and specificity of the parotid biopsy are comparable with that of labial salivary glands [20] and additionally can provide evidence about LELs and well-formed lymphoid follicles or germinal centers (GC). Theander and colleagues (2011) suggested that the detection of GC-like structures by light microscopy in pSS diagnostic salivary biopsies is a highly predictive and easy-to-obtain marker for non-Hodgkin lymphoma (NHL) development, allowing for risk stratification of patients and the possibility to initiate preventive B-cell-directed therapy [23]. The histopathological results of a parotid biopsy can be indicative of malignant lymphoma, as MALT lymphomas often develop in the parotid gland and rarely in labial glands. Repeated biopsies from the same parotid gland offer information concerning the course of the disease.

### Table 5: Treatment of SS.

<table>
<thead>
<tr>
<th>SUPPORTIVE</th>
<th>CAUSAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Local</td>
<td>1. B-cell depletion</td>
</tr>
<tr>
<td>EYE</td>
<td>e.g. Rituximab</td>
</tr>
<tr>
<td>a. Artificial tears</td>
<td>2. Inhibition of costimulation of T-cells</td>
</tr>
<tr>
<td>b. Corticosteroids</td>
<td>e.g. Abatacept</td>
</tr>
<tr>
<td>c. Immunosuppressives</td>
<td>3. anti TNF-a</td>
</tr>
<tr>
<td>d. Sealed glasses</td>
<td>e.g. Infliximab, Etanercept</td>
</tr>
<tr>
<td>e. Blocking the lacrimal punctum</td>
<td>4. IFN</td>
</tr>
<tr>
<td>MOUTH</td>
<td>e.g. Rontalizumab</td>
</tr>
<tr>
<td>a. Artificial saliva</td>
<td>2. Systemic</td>
</tr>
<tr>
<td>b. Antifungal therapy</td>
<td>a. Pilocarpine</td>
</tr>
<tr>
<td>c. Fluoride application</td>
<td>b. Cevimeline</td>
</tr>
</tbody>
</table>

### Table 6: Top 10 Therapeutic Classes by U.S. Dispensed Prescriptions in 2011 (http://www.imshealth.com).

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Drug Class</th>
<th>Xerogenic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antidepressants</td>
<td>YES</td>
</tr>
<tr>
<td>2</td>
<td>Lipid Regulators</td>
<td>NO</td>
</tr>
<tr>
<td>3</td>
<td>Narcotic Analgesics</td>
<td>YES</td>
</tr>
<tr>
<td>4</td>
<td>Anti-diabetes agents</td>
<td>NO</td>
</tr>
<tr>
<td>5</td>
<td>ACE Inhibitors</td>
<td>YES</td>
</tr>
<tr>
<td>6</td>
<td>Beta Blockers</td>
<td>Uncommon</td>
</tr>
<tr>
<td>7</td>
<td>Respiratory Agents</td>
<td>YES</td>
</tr>
<tr>
<td>8</td>
<td>Anti-ulcerants</td>
<td>YES</td>
</tr>
<tr>
<td>9</td>
<td>Diuretics</td>
<td>YES</td>
</tr>
<tr>
<td>10</td>
<td>Anti-epileptics</td>
<td>YES</td>
</tr>
</tbody>
</table>

### Treatment

Evidence-based therapy for SS is limited and the treatment of patients with SS is mostly mainly supportive (Table 5).

Local treatment for dryness of eyes and mouth is helpful in many cases. Artificial tears lubricate dry eyes, and in case of keratoconjunctivitis local corticosteroids and local immunosuppressive may be used. Sealed glasses are also introduced in an attempt to prevent evaporation of tears and to conserve the tear film. Sealing the lacrimal uncut in the inner margin of the eyelid can also be helpful by blocking the normal drainage to the nose. To treat xerostomia, one first has to estimate whether stimulating salivary secretion by gustatory (sugar-free sweets), mechanical (chewing gum) or sialagogue medication (pilocarpine, cevimeline) results in relief of xerostomia. When stimulation of salivary secretion is uneventful, one can try to treat xerostomia with mouth rinses, artificial saliva and/or oral gels. Antifungal therapy, such as local treatment with nystatin, myconazole or amphotericin B, frequently is needed to treat oral candidiasis. Due to the increased risk of dental caries, a weekly to daily use of topical neutral fluoride applications or mouthrinses is indicated in dentate patients.

During the past two decades, biologicals have become available to target specific cells or cytokines that are fundamental in the immune response. Under this new perspective, inhibitors of TNF-, INF-, B-cell depletion therapies, BAFF-inhibitors and treatments targeting the co-stimulation of T-cells have been also recruited in the treatment of SS [24,25].

The therapeutic approach to the patients with SS and MALT lymphoma is a matter of debate [26].
Interrelation with age and sex

Studies indicate that the average intake of drugs increases with age. In U.S., for example, the intake of 1-2 drugs/day/person progressively increases from 24% to 87% from the age of 18 to the age of 65 respectively (Figure 9). The prevalence of dry mouth increases with the number of drugs taken per day (Figure 10). In a study that related the prevalence of dry mouth and age, Nederfors et al. not only confirmed the aforementioned data, but also concluded that the presence of drug-induced dryness was greater in women than men [28].

Possible mechanisms

Drugs induce oral dryness by interfering with the production of fluid and electrolytes in salivary glands, by affecting the production of proteins and high molecular weight compounds or by reducing body’s content of salt and water. This is mainly the result of their effect on neurotransmitters and receptors. Parasympathetic stimulation produces abundant saliva of low protein concentration while sympathetic stimulation produces little saliva but rich in protein, giving a sensation of dryness [29]. This section will focus on describing the mechanism upon which the most commonly used therapeutic drugs (Table 6) induce xerostomia. More detailed lists about xerogenic medication can be found in ‘www.drymouth.info’.

Antidepressants

Antidepressants were the most common drug category prescribed in 2011 in the U.S. Even more notable is the fact that over 60% of patients prescribed antidepressants report taking them for more than 2 years, and 14% for 10 years or more. Antidepressants fall into four different classes, viz. tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). TCAs are known to cause dry mouth, along with other adverse effects such as anticholinergic effects, sedation, and weight gain.

Drugs

Drugs are the most common cause of dry mouth. A review of the 200 most frequently prescribed drugs in the U.S. revealed that the most common side effect was dry mouth (80.5%) followed by dysgeusia (47.5%) and stomatitis (33.9%) [27]. The exact relationship between dry mouth and drugs is variably influenced by many factors, such as type of drug, number of drugs, drug combination, dose, form, time of intake, duration of use, drug interaction and reliability of patient’s report. The situation is even more complicated in diseases and disorders that contribute to the problem. Nonetheless, it is generally accepted that the prevalence of dry mouth increases with age and the number of drugs taken per day. Also drug-induced dry mouth is primarily reversible, and an increasing amount of drugs has the capacity to induce oral dryness, while xerostomia can occur in the absence of drugs as well.
The most commonly reported adverse event in patients on tiotropium (an anti-muscarinic agent) was dry mouth (9.3% versus 1.6% relative to placebo; p < 0.05) [35], while overall 6-13% of patients receiving it complain for xerostomia [36,37].

Cough and cold preparations
Stimulation of α- and ß-adrenergic receptors in the mucous membrane of the respiratory tract by pseudoepinephrine and phenylephrine results in the shrinking of the nasal mucous membranes and relieves nasal obstruction. Studies demonstrated that pseudoepinephrine has the capacity to induce oral dryness in 0.4-11% of patients [38,39].

Antihistamines
Three antihistamines are commonly used, viz. brompheniramine, clopheniramine and carbinoxamine. Their frequent combination with decongestants as well as breathing through mouth can cause dry mouth [38,39].

Anti-ulcerants
Anti-ulcerants are used as part of the treatment of ulcers. The two basic types of anti-ulcerants are H2-blockers and proton-pump inhibitors. Dry mouth is found in 41% of patients receiving H2-receptor antagonist for eradication of *Helicobacter pylori* [40]. Teare and co-workers reported subnormal parotid or whole saliva flow rates in patients treated with omeprazole, a common proton-pump inhibitor [41].
Diuretics
Diuretics increase the formation and extraction of urine. As a result, there is a decrease in the volume of extracellular water and a consequent reduction in cardiac output and blood pressure. Furthermore, diuretics affect the flow and electrolyte composition of saliva. According to Smidt et al., 17.8% of patients taking diuretics experience dry mouth [34]. Hebbab et al. distinguished the frequency of dry mouth in patients taking thiazide, loop and potassium sparing diuretics in 3, 8 and 16%, respectively [33].

Anti-epileptics
Anti-epileptics are a class of drugs that prevent rapid, repetitive, stimulation of the brain that causes seizure activity. According to Zaccara et al. there is a selective dose-dependent pattern in the onset of dry mouth after the administration of pregabalin, which becomes evident after a dosage of 150mg/day [42]. There are also sporadic reports of transient ‘sicca syndrome’ during phenobarbital treatment [43] or even phenytoin-induced pseudo-Sjögren’s syndrome [44]. Mild xerogenic effect has been attributed to carbamazepine, oxcarbazepine, gabapentin, valproic acid, clonazepam, zonisamide, lamotrigine, and topiramate (www.drymouth.info).

Management of drug-induced xerostomia
Drugs induced xerostomia can be prevented or diminished by avoiding xerogenic drugs or minimizing their exposure to them. Substitution of a different agent with similar therapeutic properties can usually relieve the symptoms. If this is not possible, patients should be reassured that in most cases this condition is not permanent and salivary gland function will return to pre-treatment levels after the end of the therapy. In order to support these patients, usage of salivary stimulants or usage of artificial saliva, in particular substitutes with a stimulating additive such as malic acid during daytime and gel type substitutes during night, should be encouraged during their treatment with xerogenic drugs.

Radiotherapy
Radiotherapy plays a fundamental role in the treatment of the majority of patients with head and neck cancer. It can be used as a single modality or in combination with surgery and/or chemotherapy and typically involves administration of high doses to the major salivary glands. It has to be mentioned that ablation therapy of thyroid cancer with radioactive iodine treatment can also result in radiation damage to salivary gland tissue as, besides thyroid glands, salivary glands have high uptake of this agent too.

In most cases, radiation damage to salivary gland tissue results in progressive loss of glandular function and diminished salivary output. Patients complain of oral dryness, impairment of oral functions (speech, chewing, and swallowing) because of insufficient lubrication of mucosal surfaces and of ingested food [45]. The oral mucosa can become dry and atrophic, leading to frequent ulceration and injury. The shift in oral microflora towards cariogenic bacteria in combination with the reduced saliva flow and altered saliva composition may lead in radiation caries [46,47]. It must be noted that the subjective symptom of xerostomia does not always correlate with salivary flow rates; this not only counts to radiation-induced xerostomia, but also to xerostomia from other origins.

Pathophysiology
One week after the onset of conventional radiotherapy treatment, when 5-10 Gy are typically delivered, the salivary output declines by 60-90%. The acute phase of xerostomia is characterized by thick and sticky saliva, as a result of the faster decline in the serous, watery content of the saliva, compared to the decline of mucins and proteins. Late recovery is possible in cases of moderate radiation mode [48-50]. More recent studies revealed, however, that the serous parotid and seromucous submandibular glands are probably equally sensitive to ionizing radiation [51].

The mechanism of acute salivary damage is not fully understood and to date several theories have been proposed, amongst others:

1. DNA-damage caused by radiation impairs proper cell division, resulting in cell death or senescence of cells that attempt to divide. Based on the fact that cells of salivary glands have a slow turnover rate (60-120 days), they would be expected to be late responding tissue (>60 days) [52]. However, the changes in quantity and composition of saliva occur shortly after the radiation, indicating that salivary glands respond acutely [51,53]. Radiation injury leads to the loss of saliva producing acinar cells, but ducts, although deprived of function, remain intact [54]. The study of the role of apoptotic cell death after radiotherapy came up with controversial findings. Paardenkooper et al. did not observe a dose related increase in apoptotic cells early after radiation therapy [55], whereas Avila et al. found that early radiation-induced salivary gland dysfunction resulted from p53-dependent apoptosis [56]. Currently, research focuses on very selective blocking certain areas of the parotid gland from radiation injury meanwhile guaranteeing those areas of the parotid gland where the stem cells resided (probably the main excretory ducts);

2. The leakage of granules and subsequent lysis of acinar cells have been suggested as an alternative explanation for this phenomenon [57,58]. Nevertheless, studies show no cell loss during the first days after irradiation [51,59-61].
Chapter 2

Since it reduces the dose to salivary glands (parotid, sublingual, submandibular and minor), it can contribute to the maintenance of adequate saliva flow rates and the reduction of xerostomia [63-65]. IMRT compared to 2D-radiotherapy results in a significant decrease of xerostomia (both patient- and observer-rated). However, approximately 40% of patients still complain of dry mouth [66].

A rather new technique that is yet sparsely applied in the clinic is proton radiotherapy. This technique uses charged particles (e.g., protons) instead of the currently used photons. The physical and radiobiological properties of protons allow a better dose distribution, compared with photon radiotherapy. Thus, the dose to normal tissues as well as the late side effects are minimized. The existing literature shows that the dose to critical organs can be significantly reduced, especially in patients with tumors located in the pharynx [67,68] and the paranasal sinuses [69,70] as well as in the head-and-neck patients treated with bilateral neck irradiation [71].

Agents for prevention of xerostomia or restoration of lubrication

Pilocarpine

Restoration of lubrication: Pilocarpine is a cholinergic parasympathomimetic agent, acting as an agonist at muscarinic receptors. One third to two thirds of patients with post-radiotherapy xerostomia can benefit from the administration of pilocarpine [72,73]. A dose of 5 mg t.i.d. is recommended, and up to 4 weeks might be required before maximum effect is visible. The possible mechanism involves stimulation of the residual function of the major salivary glands as well as the stimulation of the minor salivary glands, especially the ones in the palate, which have been shown to have a greater resistance to irradiation [74].

The results of post-irradiation pilocarpine disappear when patients stop using it. In order to protect salivary glands during radiotherapy and to eliminate the long-term post-irradiation treatment, administration of pilocarpine during radiotherapy is an alternative choice [75,76]. The beneficial effect of pilocarpine is depended on the dose distribution in the parotid glands and when parotid dose exceeds 40 Gy, administration of pilocarpine during radiotherapy can considerably spare parotid flow and reduce patient-rated xerostomia [77].

Amifostine

Direct radioprotection can be achieved by the use of amifostine, a scavenger of free radicals [78]. Although salivary flow is preserved when amifostine is concurrently delivered with radiation, patients continue to experience xerostomia. Intravenous administration is accompanied by several side effects (e.g., nausea, vomiting, hypotension). Furthermore amifostine might also have the undesirable effect of tumor protection. Thus, the debate continues, whether it is safe to use it in cancer patients [79].

Management

Reducing the volume of irradiated salivary glands by advanced radiotherapy techniques in combination with salivary protectors and/or stimulators can be highly beneficial for patients.

Advanced radiation delivery techniques

Prevalence rates of xerostomia after radiotherapy with conventional and more advanced techniques are shown in Figure 11, of which 3-dimensional conformal radiotherapy (3-D-CRT) and Intensity modulated radiotherapy (IMRT) are currently most commonly applied.

3-D-CRT is designed to deliver an exact dose of irradiation to a target volume. This is achieved by creating a three dimensional image of the tumor, so that multiple radiation beams can be shaped exactly to the contour of the treatment area. There is evidence that reduced radiotherapy dosages by 3-D-CRT to contralateral parotid glands result in less loss of salivary gland function post-radiotherapy up to 2 years after the completion of radiotherapy [62]. Albeit 3-D-CRT has the potential to decrease the prevalence and severity of xerostomia, xerostomia has been shown to be significantly worse after bilateral compared to unilateral treatment.

IMRT is currently recommended as a standard approach in head-and-neck cancer, as it allows a more accurate distribution of specific radiation dosage and dosage distribution to the tumor and therefore provides better sparing of the surrounding tissues.
Tempol

Tempol is stable nitroxide, providing radioprotection possibly by mimicking superoxide dismutase activity and scavenging free radicals. In a mouse model, tempol has been proven to significantly reduce salivary gland hypofunction [80], by protecting salivary glands, but not tumor tissue [81]. Thus tempol could be considered for human clinical trials.

Keratinocyte growth factor (KGF)

KGF can be administered prior or during radiotherapy. KGF suppresses apoptosis and enhances survival and proliferation of salivary acinar cells [82]. Postirradiation administration of KGF most likely accelerates expansion of the pool of progenitor/stem cells that survived the treatment.

Oral lubricants and saliva substitutes

Symptomatic approach of xerostomia is attempted when stimulation of residual secretion is insufficient or in cases there is a contra-indication in the administration of the aforementioned agents. The most commonly applied and best studied saliva substitutes are based on carboxymethylcellulose [83], mucin [84] or xantham gum [85]. Mucin- and xantham gum-containing substitutes are usually preferred because they have superior rheologic and wetting properties compared to carboxymethylcellulose-based saliva substitutes. During night and when daily activities are at a low level, gel-like saliva substitutes are preferred [86].

Adult salivary gland stem cells

Artificial lubricants and sialogogues ameliorate the consequences of hyposalivation, but their effects are at best transient. Such management techniques do not address the source of the problem: a lack of functional saliva-producing acinar cells, resulting from radiation-induced stem cell sterilization. Stem cell replacement therapy may be a good option to treat radiation-induced hyposalivation. Recent identification of salivary gland stem and progenitor cell populations provides a basis for development of a stem cell-based therapy for xerostomia to provide a more durable cure for hyposalivation [87].

Epilogue

Although not essential for the maintenance of life, saliva plays a fundamental role in the function and projection of the human body. Although not much appreciated when it is routinely found abundant in the oral cavity, its diminution leads to the very unpleasant sensation of oral dryness, to an abundance of oral complaints and to a dramatic decrease in the quality of life. Xerostomia is also a common symptom of a wide variety of diseases and conditions and the resulting complaints may point the physician to the underlying disease. While much progress has been achieved so far in the investigation of its mechanisms and treatment options, it is indisputable that there is more to be done as still xerostomia and its related complaints are hard to treat to the patients’ satisfaction.
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Chapter 3

Diagnosis