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Radiation-induced sialadenitis

Stage classification and immunohistology

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Summary. The course of radiation-induced sialadenitis in 58 cases in the salivary gland registry (Institute for Pathology of the University of Hamburg 1965-1987) was subjected to pathohistological and immunohistochemical analysis. The pathohistological changes may be classified by severity into 3 stages. Stage I is characterized by mild inflammatory interstitial changes and moderate atrophy of individual glandular acini. In Stage II there is an increase in inflammatory infiltrate in connection with fibrotic changes in the interstitium and epithelial metaplasia in the ductal system. In stage III we find cirrhotic parenchymal alteration with clear inflammatory activity and an almost complete parenchymal atrophy. Immunohistochemically, the markers for secretory gland function (immunoglobulin A, secretory components, lysozyme, lactoferrin) show an increased reaction in the ductal system during stages II and III, while the amylase reaction decreases or is absent, as would be expected with increasing parenchymal atrophy.

Keywords: radiation-induced sialadenitis, stage classification, immunohistology

The salivary glands often lie directly in the path or at the fringes of the irradiation field during radiotherapy of tumors in the head and neck region. As a result, changes may occur whose clinical and morphological picture may be summed up by the term radiation-induced sialadenitis (13).

Acute clinical symptoms of radiation-induced sialadenitis occur within minutes to several hours after the end of radiotherapy. Patients complain of pain in the affected salivary glands, swelling, and general dryness of the mouth (9, 11). These complaints may diminish or continue in the form of swallowing difficulties, loss of taste, and xerostomy (7, 14). In addition, increases in dental caries after radiation-induced salivary gland damage has been reported (1, 8, 16, 17).

Both the quantity and composition of the secreted saliva change under the influence of radiation. A significant acute decrease in saliva flow from the parotid gland occurs at a total irradiation dose between 9 Gy and 80 Gy (7, 11, 14, 16) such that there is a dose-response relationship in the reduction of the salivary flow during radiotherapy. Persistent reduction in salivary flow occurs at a total dose of 50-60 Gy. At radiation doses of 20-30 Gy an increase in glandular secretion is possible (16). Salivary glands that have been

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damaged by irradiation secrete saliva with elevated concentrations of sodium, chloride, calcium, and protein (5). Beta-adrenergic stimulated amylase secretion of serous cells in vitro is transiently decreased at as little as 20 Gy (1).

In this study, 58 cases of radiation-induced sialadenitis (from the salivary gland registry at the Institute for Pathology of the University of Hamburg (1965-1987) will undergo pathohistological and immunohistochemical analysis, and an attempt will be made to classify the resultant findings into stages based on the severity of changes in the salivary gland.

Table 1. Localization of 58 cases with radiation-induced sialadenitis (salivary gland registry 1965-1987)

Localization	*n*[a]	*%*
Submandibular gland (Sm)	41	64.5
Parotid gland (Pa)	11	17
Sublingual gland (Sl)	4	6.5
Palatine glands	2	3
Lingual glands	2	3
Buccal glands	1	1
Labial glands	1	1
Other locations	2	3

[a] 6 x additional localization Pa and Sm, 3 x Sm and Sl, each 1 x Sm and floor of the mouth or palatine and lingual glands

Table 2. Underlying diseases in 58 cases with radiation-induced sialadenitis

Underlying disease	*n*
Squamous cell carcinoma of the head-neck region	
- Floor of the mouth	15
- Tongue	15
- Facial skin and external ear	4
- Lower lip	3
- External auditory canal	2
- Tonsils	2
- Nasopharynx	2
- Oropharynx	2
- Parotid gland	1
- Larynx	1
Other carcinomas	
- Adenocarcinoma Sm	1

- Adenoid cystic carcinoma Pa	1
- Papillary thyroid gland carcinoma	1
- Bronchial carcinoma	1
- Mammary carcinoma	1
Other tumors	
- Melanoma	1
- Invasive fibroma	1
- Lymphogranulomatosis	1
- Soft tissue sarcoma	1
No further information	2

Table 3. Stage classification of radiation-induced sialadenitis

Pathohistological characteristics	Stage			
	I	II	III	
Glandular acini				
- Swelling	+	(+)	-	
- Vacuolization	+	(+)	-	
- Atrophy	(+)	+	+++	
Salivary duct system				
- Ectasia	(+)	+	++	
- Squamous cell metaplasia	-	+	++	
- Goblet cell metaplasia	(+)	+	++	
- Ductular proliferation		-	+	++
Glandular interstitium				
- Periductal fibrosis	(+)	+	++	
- Periductal sclerosis	-	-	++	
- Periductal lymphocytic infiltration	(+)	+	++	
- Periductal mucous exudation	-	(+)	+	
- Mucosal granuloma	(+)	+	+	
- Lipomatosis				
Vascular system				
- Scleroses	-	+	++	
- Stenoses	-	(+)	+	
Lobular transformation				
(Salivary gland cirrhosis)	-	(+)	++	

Materials and methods

The localization of the 58 cases of radiation-induced sialadenitis that were studied are presented in Table 1. The underlying diseases that led to radiotherapy are listed in Table 2.

After fixation with formalin, the paraffin sections were prepared and stained using the following: Hematoxylin-eosin (HE), PAS reaction, Astra blue, and van Gieson elastica stain. The PAP method was used on the same material to detect the following secretion products: Immunoglobulin A, G, and M (IgA, IgG, IgM); secretory components; lysozyme; lactoferrin; S-100 protein (all rabbit, DAKO Corp.); and amylase (rabbit, SIGMA Corp.). The extent of the tissue changes was classified using a semiquantitative scale (-, [+], +, ++, +++). Expression of the secretion products noted above was recorded in the same way.

Results

The pathohistological changes in the irradiated salivary glands may be classified into three stages (Table 3).

Stage I is characterized by marked swelling and vacuolization of the serous glandular acini. Moderate atrophy of isolated glandular acini may be observed in several regions. The periductal tissue is permeated by a small amount of lymphocytic infiltrate and exhibits moderate fibrosis.

Significant parenchymal reduction may be observed in Stage II (Figure 1) as a result of atrophy of glandular acini. In addition to ectasia of the excretory ducts one also observes moderate ductal proliferation. The dilated ductal lumina are filled with secretion. Moderate periductal fibrosis and significant lymphocytic infiltration are also observed. Interstitial lipomatosis occurs in some areas. The blood vessels exhibit only minor sclerotic changes.

Stage III (figures 2, 3, and 4) is characterized by high-grade parenchymal reduction. The periductal tissue exhibits extensive lymphocytic infiltrate. In addition to ductal ectasia, numerous ductal proliferations are now also found. Goblet cell and squamous cell metaplasia may also develop in the ductal epithelium. In addition to an intraluminal accumulation of secretions, isolated periductal mucosal excretion changing over to mucosal granuloma may be observed. The gland lobules exhibit interstitial sclerosis. A further increase in interstitial connective tissue results in a picture of glandular transformation of the cirrhotic salivary gland type. Significant proliferation of the intima with the formation of vascular stenoses may be observed.

Characteristic immunohistochemical reactions may be detected that parallel the severity of the changes.

Figure 1. Radiation-induced sialadenitis of the parotid gland (Stage II): Focal reduction of the glandular parenchyma; moderate interstitial fibrosis and lipomatosis; small quantity of lymphocytic interstitial infiltration. HE x 85.
Figure 2. Radiation-induced sialadenitis of the submandibular gland (Stage III): Complete reduction of the glandular parenchyma; significant interstitial, primarily periductal, sclerosis; ductal ectasia as well as focal lymphocytic infiltration. HE x 85.
Figure 3. Radiation-induced sialadenitis of the submandibular gland (Stage III): Ductal proliferation with moderate ductal ectasia; significant interstitial sclerosis and lymphocytic infiltration. HE x 85.

Figure 4. Radiation-induced sialadenitis of the submandibular gland (Stage III): Significant ductal ectasia with epithelial metaplasia; periductal sclerosis and lymphocytic infiltration. HE x 85.
Figure 5. Radiation-induced sialadenitis of the parotid gland (Stage I): Clear evidence of amylase in the glandular acini; moderate vacuolization of the ductal epithelium. PAP technique x 210.
Figure 6. Radiation-induced sialadenitis of the submandibular gland (Stage II): Focal evidence of lysozyme. PAP technique x 210.
Figure 7. Radiation-induced sialadenitis of the parotid gland (Stage III): Evidence of secretory components in the distended ductal lumina and in the ductal epithelium. PAP technique x 210.
Figure 8. Radiation-induced sialadenitis of the submandibular gland (Stage III): Increased evidence of secretory components both in the distended ductal lumina and in the partially metaplastic ductal epithelium. PAP technique x 85.
Figure 9. Radiation-induced sialadenitis of the parotid gland (Stage III): Clear evidence of lactoferrin in ductular formations. PAP technique x 210.
Figure 10. Radiation-induced sialadenitis of the parotid gland (Stage III): Ductular proliferation with evidence of lactoferrin in the ductal lumina as well. PAP technique x 210.

In Stage I (Figure 5) the expression pattern of the analyzed secretion products is largely unchanged in comparison to non-irradiated salivary glands. IgA and the secretory components are primarily localized in the intercalated and striated ducts. IgM was not detected in any of the study cases. The expression of amylase, lysozyme, or lactoferrin was largely normal. S-100 protein was expressed by myoepithelial cells at the outer surface of the glandular acini and intercalated ducts.

In Stage II (figures 6, 7) one observes and increased immunocytochemical reaction for IgA, IgG, secretory components, lactoferrin, and lysozyme in the intercalated and striated duct epithelia. In addition, these secretion products may also be detected in the lumina of the salivary ducts. Amylase content in the ductal acini, by contrast, was reduced, particularly in the atrophied ductal acini.

In Stage III (figures 8, 9, 10), secretory components, lysozyme, and lactoferrin in particular are expressed in the intercalated and striated ducts. By contrast, the reactions for amylase and S-100 protein came back negative.

The immunohistochemical findings are summarized in Table 4; the stage distribution of the various salivary glands in Table 5. The frequency distribution, particularly the elevated localization in the submandibular gland, results from the fact that the salivary gland tissue came primarily from neck dissection surgery, which almost always contains submandibular tissue.

Table 4. Immunohistochemical findings in the three stages of radiation-induced sialadenitis

Secretion products	Stage

	I	II	III
IgA	+	++	+
IgG	(+)	+	(+)
IgM	-	-	-
Secretory components	+	++	++
Amylase	++	+	-
Lysozyme	+ +	+++	+++
Lactoferrin	+	+++	+++
S-100 protein	+	(+)	-

Table 5. Stage distribution of radiation-induced sialadenitis in terms of the various localizations

Stage	Parotid gland	Mandibular gland	Sublingual gland	Small salivary glands
I	5	14	2	2
II	6	14	2	4
III	-	13	-	2

Discussion

The serous parotid gland is considerably more radiation-sensitive than the submandibular gland with its sero-mucous structure or the purely mucous sublingual gland (1, 4, 6, 11, 15). The same applies to the salivary glands of rodents (2, 4, 6, 15). In addition, the enzyme content of the acinar cells at the time of a radiation plays a significant role in the extent of irradiation damage. Thus, the serous acinar cells of the rat submandibular, which have a large quantity of enzyme granules, exhibit significant radiation damage after irradiation with 50 Gy. By contrast, serous gland cells with a low number of granules do not. So-called interphase cell death occurs in serous gland cells after irradiation (17). One possible explanation under discussion for the pathogenesis of radiation damage is that heavy metals (zinc, manganese, iron) cause membrane lipid peroxidation by means of a redox system, thereby inducing membrane damage which over time leads to the release of lytic enzymes and ultimately to autolysis of the acinar cells. In addition, the membrane damage causes an increase in the calcium inflow into the acinar cells (1, 6). The elevated calcium inflow, in particular into the mitochondria, blocks cell respiration and accelerates cell death. Further changes in the form of damage to nerve endings with swelling of the axons, neurofilament lysis, and decreases in the synaptic vesicles have been observed on electron microscopy. This results in a neurosecretory dysfunction with secretory disturbance of the glandular acini (4). A primary vascular cause of the radiation-induced parenchymal damage is, by contrast, viewed as unlikely (12, 18).

Radiation-induced parenchymal damage may be classified into three stages according to severity. Stage I corresponds to an acute response to relatively low-level irradiation (20-30 Gy) that lasts only several days, as has been described by other authors in humans

(14, 16), rhesus monkeys (17), and rats (4). The largely regular expression pattern of secretion products (10) in Stage 1 in the material we studied also indicates a low level of damage to the glandular tissue. As a result, glandular tissue may restore itself when the irradiation dose is low and parenchymal damage minor. Stage II corresponds to experimental changes observed after higher irradiation doses (up to 75 Gy) (17, 18). Increased expression of the secretion products IgA, secretory components, lactoferrin, and lysozyme parallels the increased inflammatory activity, as has been described for other forms of chronic sialadenitis (3). The resultant changes are no longer completely reversible, but cause functional loss in the glandular tissue (16, 17, 18). Stage III is characterized by severe chronic sclerotic inflammation brought about by high irradiation doses, which leads to cirrhosis of the salivary glands as the end-stage of radiation damage. Such changes are observed most frequently after more than three months and after high irradiation doses (16, 17). Amylase reaction is largely negative as would be expected given the atrophy of the serous glandular tissue. The resultant changes are absolutely irreversible and are associated with permanent damage with significantly limited glandular secretory function.

Our stage classification according to the degree of severity of the inflammatory process and the destruction of gland structure associated with it correlates well with the clinical symptoms of irradiation damage to the salivary glands and with the prognosis of late radiation-induced sequelae.

Literature

All literature in English

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