SMJ Saratov Medical Journal
ISSN 2712-8253, Saratov Medical Journal
2026. Volume 7. Issue 3. Article CID e0302
DOI: 10.15275/sarmj.2026.0302

Original article

Reprint

Expression of matrix metalloproteinase-9 in the tissue and tear fluid of patients with lacrimal gland tumors

Anush G. Amiryan [1] ✉, Svetlana V. Saakyan [1, 2], Maria Yu. Gusakova [1], Olga V. Beznos [1], Tatiana A. Pavlenko [1]
✉ amiryan@yandex.ru

[1] Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia
[2] Russian University of Medicine, Moscow, Russia

Received 13 May 2026, Accepted 19 June 2026

© This article is an open access publication. Russian Text published in the *Saratov Journal of Medical Scientific Research*, 2026; 22(3): 295-301. https://doi.org/10.15275/ssmj2203295 ISSN 1995-0039.

Abstract:
Objective: To determine the diagnostic and pathogenetic significance of matrix metalloproteinase-9 (MMP-9) in various lacrimal gland tumors (LGTs) by analyzing its levels in tear fluid (TF) and tumor tissue.
Materials and Methods: The study included 35 patients with LGTs: lacrimal gland carcinoma (LGC; *n*=10), pleomorphic adenoma (PA; *n*=8), and lacrimal gland lymphoma (LGL; *n*=17). The control group consisted of 18 healthy volunteers. MMP-9 concentration was measured using enzyme-linked immunosorbent assay (ELISA) in the TF of both eyes and in tumor tissue homogenates.
Results: Elevated MMP-9 levels were observed in the TF of both eyes in patients with malignant LGTs vs. the control group, with the increase being more pronounced in LGC group. In PA cases, MMP-9 elevation was noted only on the side of the tumor, compared with the control group. In tumor tissue homogenates, the highest MMP-9 values were found in LGL group, intermediate values were observed in PA group, and the lowest values were characteristic of LGC group.
Conclusion: MMP-9 levels in TF reflect local proteolytic activity in LGTs and hold diagnostic significance, particularly regarding malignant morphological variants. The specific patterns of tissue MMP-9 expression and the lack of complete correspondence with changes in TF suggest a pathogenetic role for this enzyme in remodeling the tumor microenvironment.

Keywords: lacrimal gland tumor, tear fluid, matrix metalloproteinase-9, enzyme-linked immunosorbent assay, biomarker.

Cite as: Amiryan AG, Saakyan SV, Gusakova MYu, Beznos OV, Pavlenko TA. Expression of matrix metalloproteinase-9 in the tissue and tear fluid of patients with lacrimal gland tumors. *Saratov Medical Journal* 2026; 7(3): e0302. https://doi.org/10.15275/sarmj.2022.0101

Introduction

Extracellular matrix remodeling is among the key processes ensuring a tumor's capability of invasive growth and its tendency to cause infiltrative lesions in surrounding tissues. The balance between the synthesis and degradation of matrix components determines tissue structural organization, the conditions for cell migration, and the characteristics of the tumor microenvironment formation, which significantly affects the course of the neoplastic process [1].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases responsible for chemical decomposition of collagens, proteoglycans, and basement membrane components. They play a pivotal role in the proteolytic cascade [1, 2]. Of them, MMP-9 is considered among the most biologically active enzymes. It is involved not only in extracellular matrix decomposition but also in regulating the inflammatory response, angiogenesis, and intercellular interactions within tumor tissue [3]. MMP-9 activation is associated with the development of an aggressive tumor phenotype and changes in the tumor microenvironment, a phenomenon confirmed across various types of malignant neoplasms [4–6].

Lacrimal gland tumors (LGTs) constitute a heterogeneous group of neoplasms. It comprises both benign and malignant epithelial and nonepithelial forms, varying in their clinical course and biological behavior (*Figure* 1). Malignant LGTs – specifically lacrimal gland carcinoma (LGC) – are characterized by infiltrative growth, perineural spread, and a high risk of recurrence, which underscore the importance of the molecular mechanisms behind the invasive potential of the tumor tissue [7, 8]. However, the implementation of the MMP-9 proteolytic activity is not just tissue-based, but also locally secretory in nature, making it relevant to study biological fluids that are in direct contact with the tumor site [9].

Tear fluid (TF) is a complex, multifactorial biological medium that reflects local inflammatory, immune, and metabolic processes within the structures of the eye and its orbit. In cases of lacrimal gland pathology, TF can serve as an indicator of changes in the tumor microenvironment by accumulating molecular markers associated with the activity of the neoplastic process [10, 11].

Despite growing interest in using TF as a source of biomarkers, the relationship between the proteolytic activity of LGT tissue and the molecular composition of TF remains

© Amiryan A.G., Saakyan S.V., Gusakova M.Yu., Beznos O.V., Pavlenko T.A., 2026

insufficiently studied [12, 13]. In particular, there is a lack of systematic research comparing MMP-9 expression in LGT tissue with its concentration in TF. In this context, a comprehensive study of MMP-9 in both tumor tissue and TF is a promising approach to a deeper understanding of the pathogenetic mechanisms of tumor growth and the search for new noninvasive diagnostic markers.

The *objective* of this study was to determine the diagnostic and pathogenetic significance of MMP-9 in various LGTs based on its levels in both TF and tumor tissue.

Materials and methods

This prospective study involved 35 patients with LGTs who were undergoing examination and treatment at the Department of Ophthalmic Oncology of the Helmholtz National Medical Research Center for Eye Diseases of the Russian Federation Ministry of Healthcare (hereafter referred to as Helmholtz NMRCED). The mean age of the patients was 60.6±14.9 years (range: 28–86 years); the gender distribution was 13 men (37.1%) and 22 women (62.9%).

Based on the morphological variant of the tumor, we identified three pathological groups: LGC (*n*=10), pleomorphic adenoma of the lacrimal gland (PA; *n*=8), and lacrimal gland lymphoma (LGL; n=17) with bilateral involvement clinically diagnosed in 17.6% (*n*=3) of cases. In all instances, the diagnosis was confirmed through morphological study. A control group consisted of 18 healthy volunteers. Exclusion criteria involved any conditions or interventions capable of affecting TF composition and MMP-9 levels, such as inflammatory or infectious diseases of the eye and orbit, recent trauma or surgery, ongoing local or systemic anti-inflammatory, antibacterial, or immunosuppressive therapy at the time of enrollment, prior treatment for the current neoplasm, severe decompensated somatic conditions, and insufficient TF volume for analysis.

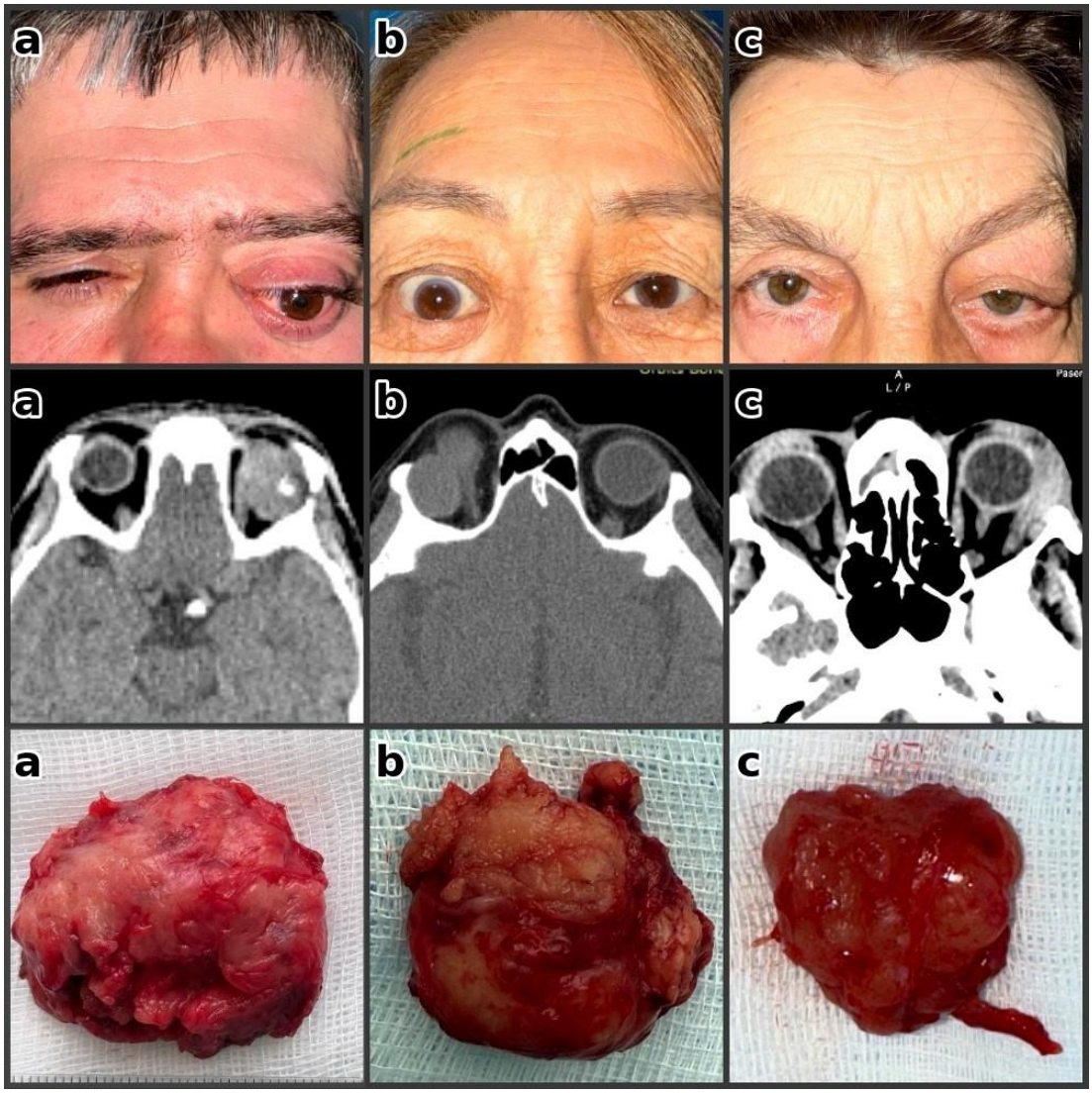


Figure 1. External appearance (*1*), CT scan (*2*), and macroscopic image of the tumor (*3*) in patients with lacrimal gland tumors: *a*, carcinoma; *b*, pleomorphic adenoma; *c*, lymphoma.

During the preoperative preparation phase, all patients underwent a standard ophthalmic examination including an assessment of orbital status, as well as computed tomography and orbital ultrasound imaging. After the clinical and instrumental assessment, and prior to the start of surgical treatment, TF samples were collected.

TF was collected using filter paper strips without prior stimulation of tear production. Samples were obtained from the inferior conjunctival fornix of both eyes during the morning hours. TF components were eluted with physiological saline at a 1:10 volume ratio. MMP-9 concentration in the eluates was determined via enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Cloud-Clone Corp., USA). MMP-9 concentration in the TF was expressed in ng/mL.

All patients underwent surgical treatment after the clinical and instrumental assessment. Under the supervision of a pathologist, a tissue fragment was obtained from the tumor removed during orbitotomy for subsequent analysis. The collected fragments were minced and homogenized in cold physiological saline, first using a manual homogenizer and subsequently an ultrasonic homogenizer (UP50H; Hielscher, Germany). The resulting homogenates were centrifuged for 10 minutes at 5,000 rpm (1,846 × g), after which the supernatant was collected for analysis. Aliquots intended for ELISA were stored at -70 °C. To assess tissue expression of MMP-9, the enzyme concentration was calculated relative to the total protein content of the tumor tissue samples and expressed in ng/mg of protein.

Additionally, we evaluated associations of MMP-9 levels in TF and tumor tissue homogenates with the clinical and morphological characteristics of the tumor, including the presence of a solid component, perineural invasion, foci of necrosis, and bone erosion, as well as clinical and anamnestic parameters, such as age, duration of the condition, and tumor volume.

Statistical data processing was performed using Microsoft Excel and IBM SPSS Statistics v.23.0 (IBM, USA). Quantitative data following a normal distribution were presented as the mean (*M*) and standard deviation (*SD*), while data following a distribution other than normal were presented as the median (*Me*) and interquartile range (*IQR*, i.e., the interval between the 25th and 75th percentiles). Nonparametric Mann–Whitney and Wilcoxon tests were used for intergroup comparisons. Relationships between variables were analyzed using Spearman's rank correlation coefficient (r_s). Differences were considered statistically significant at $p<0.05$.

This study was approved by the Ethics Committee of the Helmholtz NMRCED (Protocol No. 68/2 of June 6, 2024). All patients provided informed consent for participation in the study.

Results.

Matrix metalloproteinase-9 level in tear fluid

Analysis of MMP-9 concentration in TF revealed differences between the tumor-affected side, the clinically healthy contralateral side, and the control group. The magnitude of these differences depended on the morphological variant of the LGT (*Table* 1, *Figure* 2).

We observed the most pronounced increase of MMP-9 levels in the TF on the tumor side in patients with LGC. In them, the median enzyme concentration was 387.6 ng/mL (*IQR* 299.2), which was statistically significantly higher than the values on the contralateral healthy side and the control group data: 158.8 ng/mL (*IQR* 158.8; $p=0.02$) and 45.6 ng/mL (*IQR* 28.7; $p<0.001$), respectively. Remarkably, MMP-9 values on the contralateral healthy side in LGC patients were also statistically significantly higher than those in the control group ($p<0.001$). Besides that, a strong direct correlation was observed in LGC patients between MMP-9 levels in the TF on the tumor side and on the contralateral healthy side ($r_s=0.9$; $p=0.001$).

In patients with LGL, the median MMP-9 concentration in the TF on the tumor side was 257.1 ng/mL (*IQR* 215.9) vs. 203.9 ng/mL (*IQR* 181.1) on the contralateral healthy side ($p=0.04$). Both values significantly exceeded those of the control group ($p<0.001$ for both comparisons).

In the group of patients with lacrimal gland PA, the median MMP-9 level in the TF on the tumor side was the lowest, measuring 195.8 (*IQR* 325.8) ng/mL, compared with LGC and LGL, yet it still exceeded the control group values ($p=0.02$). On the contralateral side, the median MMP-9 concentration in TF was 152.6 ng/mL (*IQR* 381.5), which also exceeded the value observed in the control group. However, we found no statistically significant differences when comparing this value with the tumor-affected side or the control group ($p>0.05$ in all cases).

Matrix metalloproteinase-9 expression in lacrimal gland tumor tissue homogenates

When assessing MMP-9 levels in tumor tissue homogenates relative to total protein content, the highest values were discovered in LGL patients, with a median of 89.3 ng/mg protein (*IQR* 39.0). In the PA group, the median MMP-9 value in tumor tissue was 60.79 ng/mg protein (*IQR* 72.5). The lowest values of tissue MMP-9 expression were recorded in LGC cases, with a median of 39.7 ng/mg protein (*IQR* 39.9) (*Figure* 3).

When evaluating associations of MMP-9 levels in TF and tumor tissue with various clinical and morphological features with clinical anamnestic parameters, we identified no statistically significant differences or correlations: in all comparisons and correlation analyses performed, the *p*-value exceeded 0.05.

Table 1. Concentration of matrix metalloproteinase-9 in tear fluid and tumor tissue homogenates in various morphological variants of lacrimal gland tumors and in the control group, Me (IQR)

Investigated material			LGC	LGL	PA	Control group
Tear fluid, ng/mL	Side	Tumor	387.6 (299.2)	257.1 (215.9)	195.8 (325.8)	45.6 (28.7)
		Healthy	158.8 (158.8)	203.9 (181.1)	152.6 (381.5)	
Tumor tissue protein, ng/mL			39.7 (39.9)	89.3 (39.0)	60.8 (72.5)	–

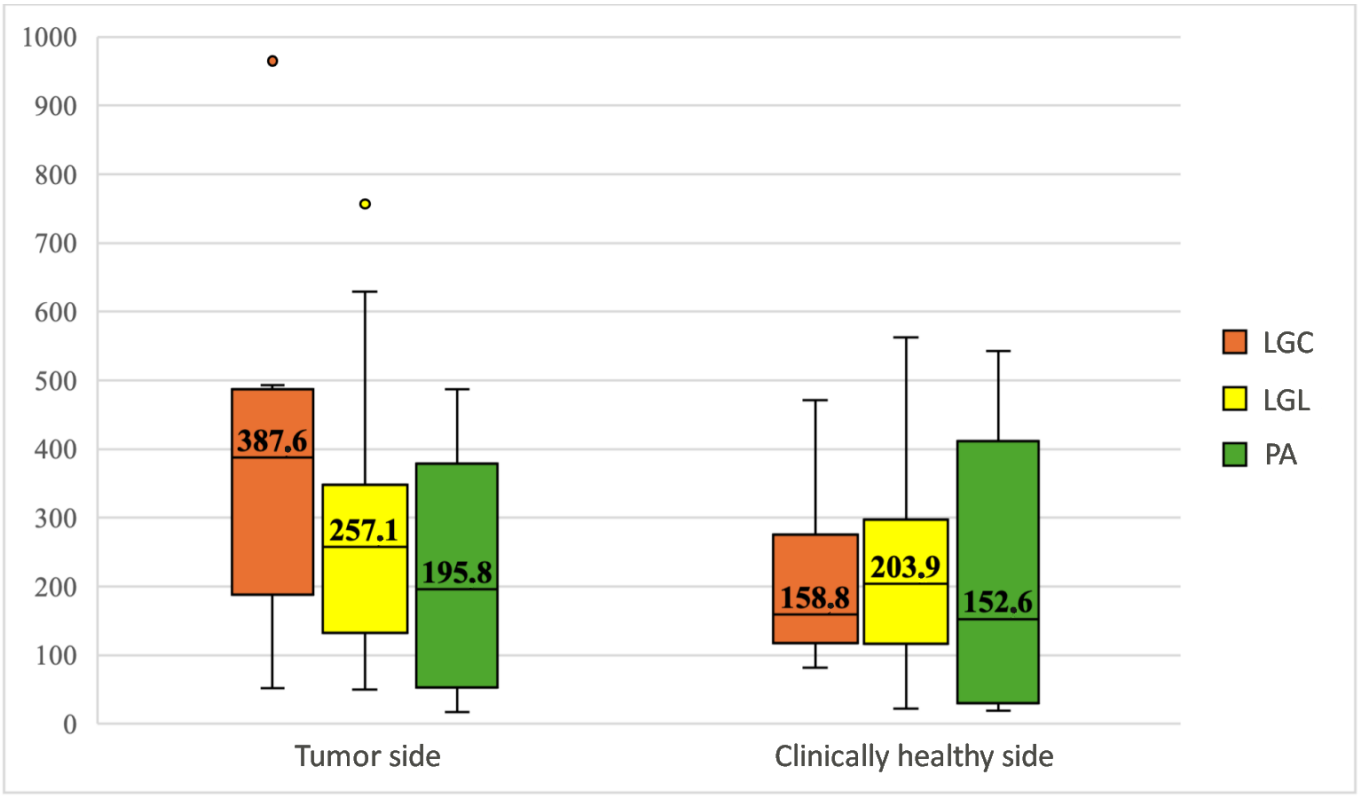


Figure 2. Boxplot of matrix metalloproteinase-9 levels in tear fluid in cases of lacrimal gland carcinoma (LGC), lymphoma involving the lacrimal gland (LGL), and pleomorphic adenoma (PA): Tumor side and clinically healthy side.

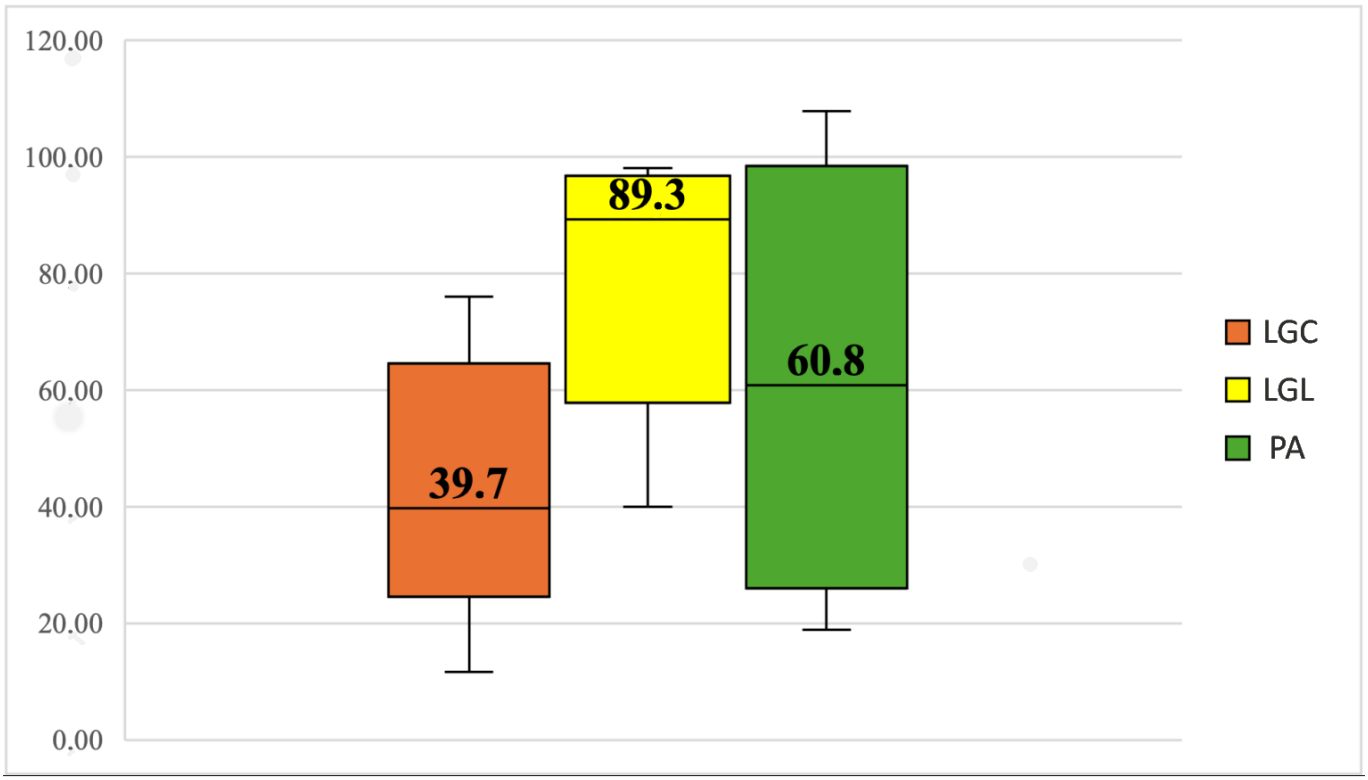


Figure 3. Boxplot of matrix metalloproteinase-9 levels in tumor tissue homogenates from lacrimal gland carcinoma, lymphoma involving the lacrimal gland, and pleomorphic adenoma side.

Discussion

MMP-9 is a key mediator of carcinogenesis, involved in processes such as tumor invasion, angiogenesis, and the development of metastatic potential. The significance of MMP-9 in carcinogenesis was confirmed by numerous clinical studies and meta-analyses. For instance, a meta-analysis involving over 2.5 thousand ovarian cancer patients discovered that increased MMP-9 expression is associated with an aggressive course of the disease, its advanced stages, lymph node metastases, and a poor survival prognosis [4]. In their study, H. Zhang et al. [5] reported elevated serum MMP-9 levels in lung cancer patients, compared with controls; these levels correlated with various clinical characteristics, including tumor/node/metastasis (TNM) stage, tumor cell differentiation grade, lymph node involvement, and smoking status. Analyzing MMP-9 expression across a wide range of malignant neoplasms, Y. Zeng et al. demonstrated that expression levels were high in many tumor types as compared with normal tissues [6]. Furthermore, the strength of expression varied by disease stage and was associated with a poor prognosis in certain malignancies, such as adrenocortical carcinoma and clear-cell renal cell carcinoma.

In ophthalmic oncology, MMP-9 attracts attention as a potential diagnostic and prognostic marker. Analyzing publicly available genomic databases, T. Wang et al. [14] demonstrated that MMP-9 possesses significant prognostic ability in patients with uveal melanoma and its expression in uveal melanoma tissues correlates with patient survival rates, thereby suggesting that this enzyme could serve as a potential prognostic biomarker and a promising target for future research. These findings align with data from colleagues in Novosibirsk, who demonstrated that in cases of uveal melanoma, MMP-9 levels in the TF on the side of the tumor correlate with levels on the contralateral side and are also linked to MMP-9 concentrations in the intraocular fluids [15]. In conjunctival melanoma, MMP-9 overexpression was detected in tumors over 1.5 mm thick, which the authors interpreted as a possible indication of the enzyme's involvement in tumor progression at later stages [16]. Studies on retinoblastoma linked increased MMP-9 expression in tumor tissue to optic nerve invasion and the clinical stage of the disease [17]. MMP-9 expression in tumor tissue was also described in intraocular lymphomas, where it is associated with mechanisms of infiltrative growth [18]. Regarding LGTs, there is a limited number of studies evaluating MMP-9 expression. Specifically, in cases of adenoid cystic carcinoma of the lacrimal gland, immunohistochemically detected MMP-9 expression in tumor tissue is associated with the histological subtype (including cribriform/tubular and solid variants), as well as with clinical signs of an aggressive course [19].

We conducted the first study of MMP-9 levels in the lacrimal glands of patients with LGTs and demonstrated that the intensity of enzyme expression varies across the tumor's morphological types. Higher MMP-9 expression in malignant processes was noted on the side of the tumor. Notably, in cases of LGC, the highest concentrations of the marker and the most pronounced asymmetry vs. the contralateral side were recorded on the tumor side. This aligns with the role of MMP-9 in extracellular matrix remodeling and the reduction of the basement membrane's barrier function. These processes that facilitate cell migration and support the invasive infiltrative growth of the tumor. The less pronounced asymmetry between the tumor side and contralateral side observed in LGL vs. LGC may reflect the specific nature of lymphoproliferative lesions, which are characterized by a more diffuse infiltrative pattern and a significant contribution of immune microenvironment cells to proteolytic activity. Statistically insignificant increase in MMP-9 levels on the tumor side in patients with PA, combined with the absence of statistically significant asymmetry between sides, may be attributed to the benign nature of the tumor process and a reduced need in thorough matrix remodeling.

The results of MMP-9 analysis in tumor tissue complement data obtained from the lacrimal gland and demonstrate that the tissue profile of this enzyme may not mirror its profile in the lacrimal gland since MMP-9 levels are determined by the contributions of multiple cell populations, and MMP-9 concentrations can vary significantly across different structural zones of the tumor. As noted by F. Briest et al., throughout the processes of tumorigenesis and progression, tumor cells are in continuous functional interaction with the surrounding connective tissue and extracellular matrix. Moreover, MMPs are frequently produced not only by tumor cells but also by cells within the microenvironment, including fibroblasts and macrophages, and proteolysis contributes to tumor progression via both matrix remodeling and the release of growth factors from the matrix [20]. Consequently, in cases of LGL, tissue MMP-9 levels may be higher due to a pronounced immune cell component and reactive infiltrate, while in LGC, MMP-9 expression may be focal, peaking in zones of invasion and tumor-stroma interaction, which is obscured when analyzing tissue homogenates.

We hypothesize that MMP-9 concentration in TF possibly reflects the overall activity of the proteolytic cascade within the tumor microenvironment, resulting from the combined contributions of tumor cells and stromal inflammatory cells. This hypothesis is supported by the absence of statistically significant associations between MMP-9 levels and specific clinical and morphological features or anamnestic data. It should also be noted that the composition and functional characteristics of the microenvironment are variable and can differ much depending on the morphological type of the tumor, degree of its differentiation, and specific cellular interactions (factors capable of modifying MMP-9 levels).

Conclusion

Our data confirm the diagnostic significance of determining MMP-9 levels in TF as a noninvasive marker of tumor-associated proteolytic activity in LGTs, particularly in their malignant morphological variants. Tissue expression of MMP-9 varied across morphological types of the tumor and did not fully mirror the changes observed in TF. Thus, TF may be considered a more sensitive biological substrate for reflecting local proteolytic activity in LGTs, whereas the analysis of tumor tissue complements the insight into the pathogenetic mechanisms underlying the remodeling of the tumor microenvironment.

Conflict of interest

None declared.

Author contributions

All authors contributed equally to the preparation of the manuscript.

Informed consent for publication

Patients signed a voluntary informed consent form for the publication of medical information.

Funding

No external funding for conducting the research and publication of the article was provided.

Compliance with ethical principles

The study protocol was approved by the institutional Ethics Committee. Approval and procedures for the protocol were obtained according to the principles of the Declaration of Helsinki.

References

1. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer* 2002; 2(3): 161-174. https://doi.org/10.1038/nrc745.
2. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: Regulators of the tumor microenvironment. *Cell* 2010; 141(1): 52-67. https://doi.org/10.1016/j.cell.2010.03.015.
3. Augoff K, Hryniewicz-Jankowska A, Tabola R, Stach K. MMP9: A tough target for targeted therapy for cancer. *Cancers (Basel)* 2022; 14(7): 1847. https://doi.org/10.3390/cancers14071847.
4. Li LN, Zhou X, Gu Y, Yan J. Prognostic value of MMP-9 in ovarian cancer: A meta-analysis. *Asian Pac J Cancer Prev* 2013; 14(7): 4107-4113. https://doi.org/10.7314/apjcp.2013.14.7.4107.
5. Zhang H, Zhao B, Zhai ZG, et al. Expression and clinical significance of MMP-9 and P53 in lung cancer. *Eur Rev Med Pharmacol Sci* 2021; 25(3): 1358-1365. https://doi.org/10.26355/eurrev_202102_24844.
6. Zeng Y, Gao M, Lin D, et al. Prognostic and immunological roles of MMP-9 in pan-cancer. *Biomed Res Int* 2022; 2022: 2592962. https://doi.org/10.1155/2022/2592962.
7. von Holstein SL. Tumours of the lacrimal gland. Epidemiological, clinical and genetic characteristics. *Acta Ophthalmol* 2013; 91 Thesis 6: 1-28. https://doi.org/10.1111/aos.12271.
8. Andreasen S, Esmaeli B, Holstein SL, et al. An update on tumors of the lacrimal gland. *Asia Pac J Ophthalmol (Phila)* 2017; 6(2): 159-172. https://doi.org/10.22608/APO.201707.
9. Roy R, Yang J, Moses MA. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. *J Clin Oncol* 2009; 27(31): 5287-5297. https://doi.org/10.1200/JCO.2009.23.5556.
10. Neroev VV, Saakyan SV, Katargina LA, et al. Features of the composition of cytokines of various biological effects in patients with uveal melanoma: local changes in the lacrimal fluid. Part 1. *Ophthalmology in Russia* 2022; 19(1): 156-166. (In Russ.) https://doi.org/10.18008/1816-5095-2022-1-156-166.
11. Ang T, Tong JY, Quigley C, Selva D. Tear inflammatory cytokine profiles in orbital inflammatory disease. *Exp Eye Res* 2025; 251: 110205. https://doi.org/10.1016/j.exer.2024.110205.
12. Yue H, Meng FX, Zhang R, Qian J. Preliminary proteomic analysis of human tears in lacrimal adenoid cystic carcinoma and pleomorphic adenoma. *Int J Ophthalmol* 2023; 16(6): 841-848. https://doi.org/10.18240/ijo.2023.06.02.
13. Zhou L, Seah LL, Chee E, et al. Integrating transcriptomics and proteomics of human lacrimal gland and tear fluid. ARVO Annual Meeting. *Investigative Ophthalmology & Visual Science* 2008; 49: E-Abstract 5297.
14. Wang T, Zhang Y, Bai J, et al. MMP1 and MMP9 are potential prognostic biomarkers and targets for uveal melanoma. *BMC Cancer* 2021; 21(1): 1068. https://doi.org/10.1186/s12885-021-08788-3.
15. Chernyavskaya MA, Efremov AV, Chernykh VV, et al. Matrix metalloproteinase-9 levels in tear fluid and intraocular fluid in choroidal melanoma. *Siberian Scientific Medical Journal* 2015; 35(3): 16-20. (In Russ.) https://www.elibrary.ru/twlrlt.
16. Kim HK, Chae SW, Woo KI, Kim YD. Expression of matrix metalloproteinase (MMP)-2, MMP-9, and tissue inhibitor of MMP (TIMP)-1 in conjunctival melanomas and clinical implications. *Jpn J Ophthalmol* 2010; 54(3): 221-226. https://doi.org/10.1007/s10384-009-0793-1.
17. Long H, Zhou B, Jiang FG. Expression of MMP-2 and MMP-9 in retinoblastoma and their significance. *Int J Ophthalmol* 2011; 4(5): 489-491. https://doi.org/10.3980/j.issn.2222-3959.2011.05.06.
18. Fukutsu K, Kase S, Iwata D, et al. The expression of matrix metalloproteinases in eyes with intraocular lymphoma. *Ocul Immunol Inflamm* 2022; 30(7-8): 1798-1802. https://doi.org/10.1080/09273948.2021.1957122.
19. Zhang L, Zhang H, Song GX, et al. The expression of MMP-2 and MMP-9 in adenoid cystic carcinoma of lacrimal gland. *Zhonghua Yan Ke Za Zhi* 2013; 49(1): 5863. (In Chinese). https://pubmed.ncbi.nlm.nih.gov/23601468.
20. Briest F, Berndt A, Clement J, et al. Tumor-stroma interactions in tumorigenesis: Lessons from stem cell biology. *Front Biosci (Elite Ed)* 2012; 4(5): 1871-1887. https://doi.org/10.2741/509.

Authors:

Anush H. Amiryan – DSc (Medicine), Principal Researcher, Division of Ophthalmic Oncology and Radiology; Assistant Professor, Department of Continuing Medical Education, Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia. https://orcid.org/0000-0002-9284-4838;

Svetlana V. Saakyan – DSc (Medicine), Professor, Corresponding Member of the Russian Academy of Sciences, Head of the Division of Ophthalmic Oncology and Radiology, Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia; Russian University of Medicine, Moscow, Russia. https://orcid.org/0000-0001-8591-428X;

Maria Yu. Gusakova – PhD Student, Division of Ophthalmic Oncology and Radiology, Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia. https://orcid.org/0009-0004-2585-7518;

Olga V. Beznos – Researcher, Division of Pathophysiology and Biochemistry, Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia. https://orcid.org/0000-0001-7557-4955;

Tatiana A. Pavlenko – PhD (Medicine), Head of the Division of Pathophysiology and Biochemistry, Helmholtz National Medical Research Center for Eye Diseases, Moscow, Russia. https://orcid.org/0000-0001-8032-4248.