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A 16-year retrospective study of dacryocystitis in adult patients in the Moldavia Region, Romania

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Abstract

Purpose: Chronic dacryocystitis (CD) is an inflammation of the lacrimal sac and nasolacrimal duct with a long-standing evolution. The aims of this study were to analyze the epidemiology and to evaluate the histopathological features and the chronic inflammation score (CIS) system of chronic dacryocystitis in the region of Moldavia, Romania, over a period of 16 years. *Methods*: We conducted a retrospective descriptive analysis of all pathological reports of chronic dacryocystitis from the Department of Pathology, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania, between January 1, 1999 and December 31, 2015, with the final application of CIS. We also recorded the demographic information of patients and lesion localizations. *Results*: Eighteen cases of CD were identified, with a female:male ratio of 8:1. Patient median age was 66.27 years (range 33–83 years), 55.55% being in their eighth and ninth decade of life. A non-systemized growth trend starting with 2002 could be identified. Microscopically, several histopathological features were identified, some of them being associated: epithelial lining hyperplasia with pseudopapillary folds (77.77% of the cases), epithelial invaginations in the submucosa (11.11%), squamous metaplasia (16.66%) or partial denudation (33.33%). The sac wall revealed chronic diffusion (88.88%) or nodular lymphocytic inflammation (11.11%). 5.55% of cases presented fibrosis in the lacrimal sac wall with few lymphocytes. Applying CIS system, the majority of cases (13 patients, 72.22%) were identified with moderate chronic inflammation, only one case (5.55%) pointed out a mild degree of inflammation with a CIS<3, but four (22.22%) cases showed severe inflammatory changes with a CIS>6. *Conclusions*: In our region, CD is more frequent in senior women, probably due to their deficient immune system. Histological specimens of CD are not commonly found in practice of pathologists, but when the histological sections are analyzed they reflect a multitude of aspects that need to be known in order to guide ophthalmologists in their practice. In our region, CD is more frequent in senior women, probably due to their deficient immune system and to the specific anatomy of their nasolacrimal duct. The histological appearances varied from patient to patient and even in the same patient varied from one area to another. There were histopathological changes indicating adaptive changes, which could lead to the development of malignant tumors at this level. Therefore, there is a need for patient education with CD both in terms of ophthalmic hygiene and in what regards possible complications in the absence of a regular presentation to the ophthalmologist.

Keywords: chronic dacryocystitis, epidemiology, epithelial hyperplasia, squamous metaplasia, chronic inflammation score.

Introduction

The diseases of lacrimal drainage system represent only 3% of all visits to Ophthalmology clinics [1]. Among all these disorders, dacryocystitis distinguishes itself as a frequent lesion and represents an inflammation of the lacrimal sac and nasolacrimal duct caused by the spread of microorganisms from the conjunctiva or the nasal mucosa. Usually, this disease is associated with the functional or anatomical obstruction of the nasolacrimal duct, as the lacrimal sac distensions due to the accumulation of tears and mucous secretions provide an environment for conjunctival flora growth [2]. In specimens of dacryocystorhinostomy and dacryocystectomy sent by the ophthalmologist to the Department of Pathology is commonly diagnosed non-granulomatous inflammation, but benign epithelial tumors (papilloma) or malignant epithelial tumors (transitional cell carcinoma, adenocarcinoma, undifferentiated carcinoma, mucoepidermoid carcinoma) could be rarely identified and lymphoid tumors (non-Hodgkin's B-cell lymphoma), leukemic infiltration, plasmacytoma, or oncocytoma are very rare [3, 4]. However, dacryocystitis is the most common pathology of the lacrimal drainage system, representing 79–87% of all lesions (tumoral and non-tumoral) at this level [3, 5].

In this study, we aim to analyze the epidemiology and to evaluate the histopathological features and the chronic inflammatory score (CIS) system of chronic dacryocystitis

(CD) in the region of Moldavia, Romania, over a period of 16 years, as this pathology has not been investigated in Romania up to now and also because we try to investigate if there occurred any changes in their histopathological characteristics over time as very few articles dealing with this issue have been published in the literature in the field.

Patients, Materials and Methods

A retrospective descriptive analysis of all pathological reports of chronic dacryocystitis between January 1, 1999 and December 31, 2015 was carried out based on the files of the Department of Pathology, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania. For each case, we also recorded the demographics of patients and lesion localizations. Histopathological blades were obtained after processing the tissue specimens with standard histological technique. The specimens were fixed in 4% (*v/v*) formalin, hardened in a mixture of acetone and xylene, and embedded in paraffin. Four µm thick serial sections were cut and stained with Hematoxylin–Eosin (HE). In some cases, the immunohistochemical two-step staining technique using the EnVision™+ and anti-cytokeratin (CK) AE1/AE3 antibody was applied. The pathologist examined the lumen, the lining epithelium and the lacrimal sac wall searching for chronic inflammatory cell infiltration, fibrosis and capillary proliferation. A chronic inflammation score was assigned to all cases based on the severity of the inflammation [6]. The histopathological features were graded as follows: (*1*) The intensity of inflammatory cell infiltration [number of inflammatory cell in a high-power field (HPF)] was considered to be mild: <50 cells, moderate: 50–200 cells, severe: >200 cells; (*2*) The degree of capillary proliferation (number of capillary vessels in a HPF) was reviewed as mild: <5, moderate: 5–10, severe: >10; (*3*) The density of fibrosis (the amount of fibrotic tissue in a HPF) was assumed to be mild: <25%, moderate: 25–50%, severe: >50%; in order to determine the intensity of chronic inflammation in the lacrimal sac wall, all these three histopathological features were scored individually by their severity (mild = 1, moderate = 2, and severe = 3). After that, a total score (sum) was obtained for each case ranging between 3 and 9 and named "chronic inflammatory score" (CIS). Finally, every case was grouped according to its CIS as: mild chronic inflammation (CIS<3), moderate chronic inflammation (3<CIS<6) and severe chronic inflammation (CIS>6).

Results

From a total of 768 cases received over a 16-year period in the Department of Pathology, 18 (2.34%) cases were patients with CD (Figure 1) due to primary acquired nasolacrimal duct obstruction, who were treated by means of external dacryocystorhinostomy or dacryocystectomy in the 2nd Ophthalmology Clinic of "Prof. Dr. Nicolae Oblu" Emergency Hospital, Iaşi.

The annual number of cases with CD was small, but a non-systemized growth trend starting with 2002 could be identified (Figure 2).

Female:male ratio was 8:1 (Figure 3), with a median age of 66.27 years (range 33–83 years), 55.55% of the patients being in their eighth and ninth decades of life (Figure 4).

CD affected the left lacrimal sac in 14 (77.77%) cases and the right lacrimal sac in four (22.23%) cases (Figure 5).

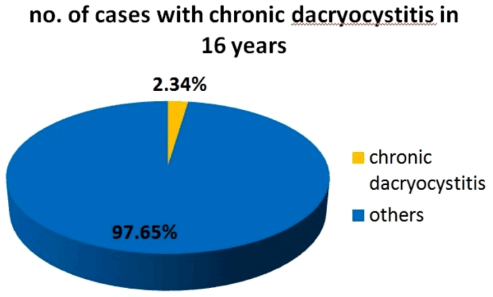

Figure 1 – ***Incidence of chronic dacryocystitis in a total of 768 cases received over a 16-year period (1999–2015) in the Department of Pathology, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania.***

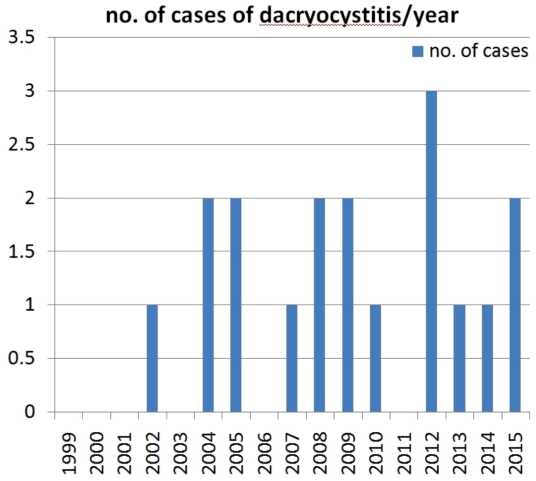

Figure 2 – ***Number of chronic dacryocystitis cases per year over a 16-year period (1999–2015).***

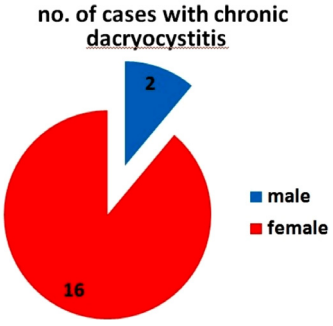

Figure 3 – ***Number of chronic dacryocystitis cases correlated with patients' gender.***

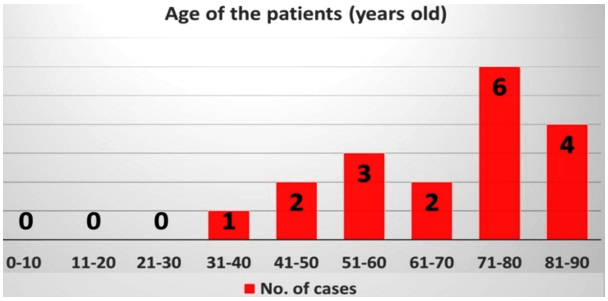

Figure 4 – ***Number of chronic dacryocystitis patients correlated with their age (years old).***

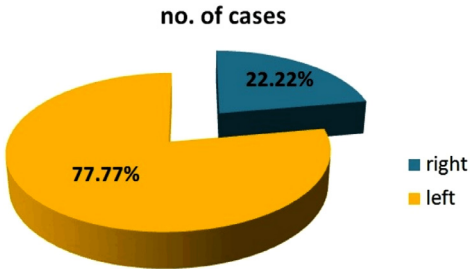

Figure 5 – ***Percentage of chronic dacryocystitis cases correlated with lesion location.***

The patients presented with a swelling in the medial angle (Figures 6 and 7). The recorded histopathological aspects revealed important changes of the lacrimal sac lumen, lining epithelium, and its lamina propria. The lacrimal sac lumen was dilated due to mucus, hemorrhage, inflammatory cells accumulation or detached epithelial papillae in 77.77% of the investigated cases (Figure 8), or it was narrowed, and 22.22% were irregular, mainly due to inflammatory changes in the lacrimal sac wall but also due to irregular folding of the lining epithelium (Figure 9).

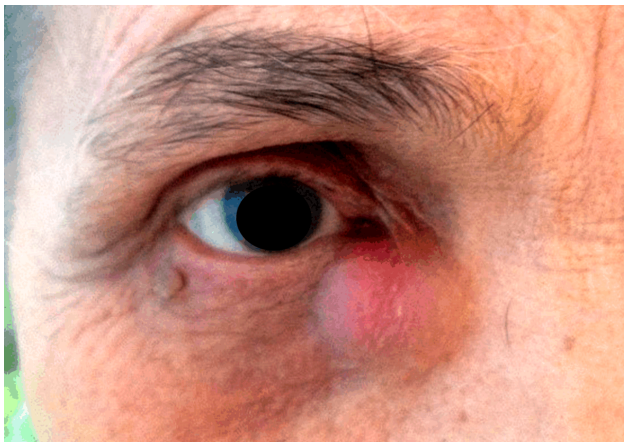

Figure 6 – ***Chronic dacryocystitis – preoperative aspect: roundness and redness swelling localized below the medial canthal ligament (private collection, Dr Claudia Florida Costea).***

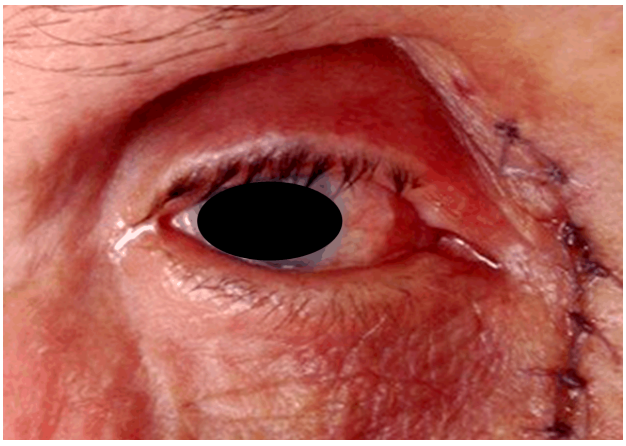

Figure 7 – ***Chronic dacryocystitis – postoperative aspect: the lesion was excised and the region returned to normal (private collection, Dr Claudia Florida Costea).***

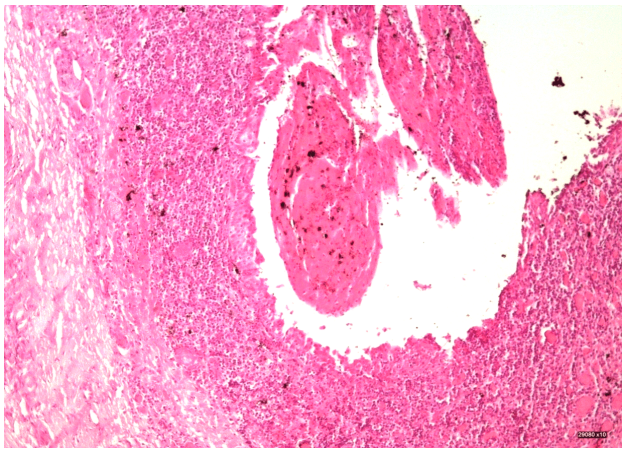

Figure 8 – ***Chronic dacryocystitis. Dilated lumen contained hemorrhage, inflammatory cells, and necrotic debris. The lacrimal sac wall presented a hyperplastic lining epithelium with some denudated areas. In lamina propria there were numerous thin-walled and distended blood vessels, and a dense inflammatory cell infiltration (HE staining, ×100).***

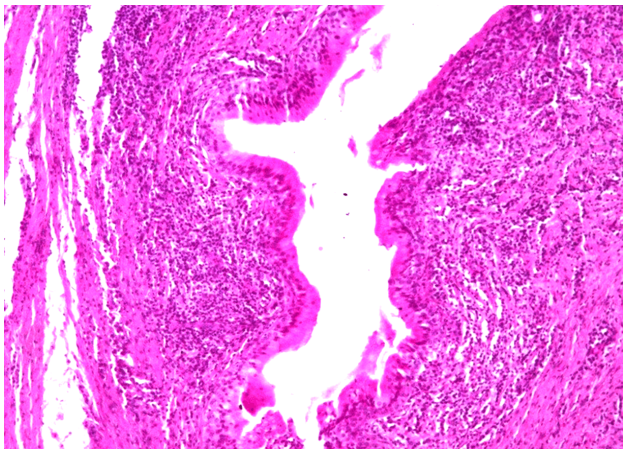

Figure 9 – ***Chronic dacryocystitis. Irregular constriction of the lumen due to abundant chronic inflammatory infiltration of the sac wall and partial hyperplasia and stratification of the epithelial lining which formed pseudopapillae (HE staining, ×100).***

We found important and variable pathological changes of the lining epithelium, such as: hyperplasia with stratification consisting of eight to 10 layers including numerous goblet cells, with the development of pseudopapillary features (in 77.77% of cases) (Figures 10 and 11), mucous metaplasia and invaginations into the lamina propria similar to Henle's glands (in 11.11% of cases) (Figures 12 and 13), squamous metaplasia (16.66% of cases) (Figures 14 and 15) or necrosis with partial denudation (33.33%) (Figures 16 and 17). Often, we found all these features in different parts of the same lesion. All cases showed, in variable degree, diffuse chronic inflammatory cells in the lacrimal sac wall (Figures 18 and 19), and proliferation of newly formed capillary vessels, also with variable degree (Figures 20 and 21). Only one case (5.55%) presented an increase in collagenous fibers and few lympho-plasmacytic cells in the lacrimal sac wall.

Regarding the intensity of chronic inflammatory cell infiltrate, we found that three (16.66%) patients had

mild (Figure 18), five (27.77%) cases moderate, and 10 (55.55%) severe infiltration (Figure 19). The degree of capillary proliferation was mild in 11 (61.11%) cases, moderate in five (27.77%) cases and severe in two (11.11%) cases (Figures 20 and 21). The density of fibrosis was mild in five (27.77%) cases, moderate in 11 (61.11%) cases (Figures 22 and 23), and severe in two (11.11%) cases (Figures 22 and 23).

Applying the chronic inflammation system, the majority of cases (13 patients, 72.22%) were identified with moderate chronic inflammation, only one case (5.55%) pointed out mild degree of inflammation with a CIS<3, but four (22.22%) cases showed severe inflammatory changes with a CIS>6. The intensity of histopathological features is illustrated in Table 1 and chronic inflammation score is shown in Table 2.

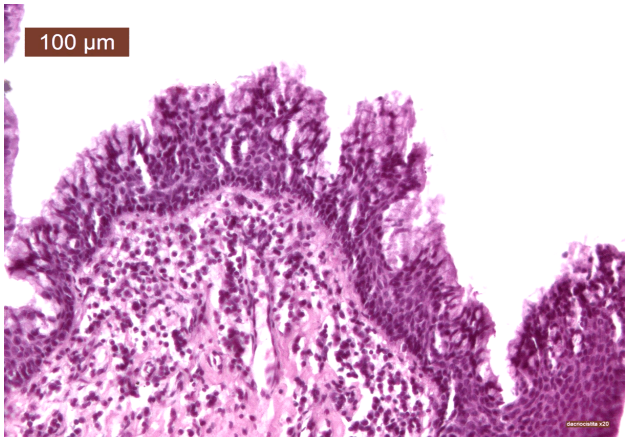

Figure 10 – ***Chronic dacryocystitis. Epithelial hyperplasia, including goblet cells, produced pluristratification with eight to 10 layers (HE staining, ×200).***

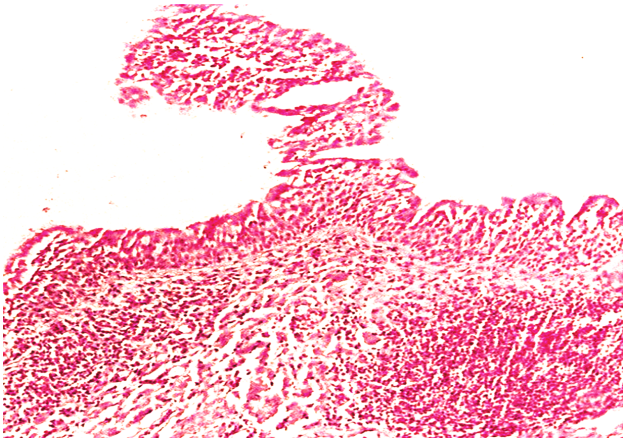

Figure 11 – ***Chronic dacryocystitis. Hyperplastic epithelium formed pseudopapillae that protruded into the lacrimal sac lumen (HE staining, ×100).***

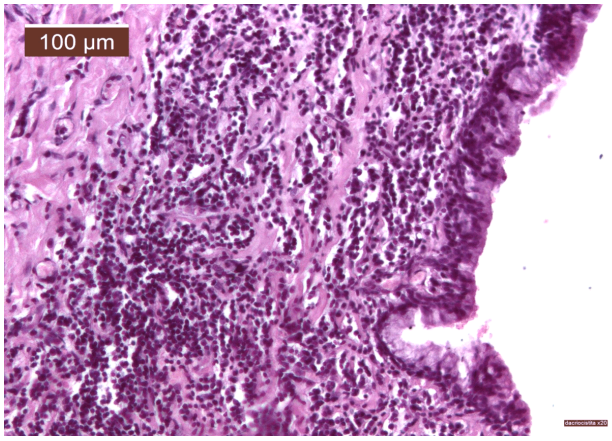

Figure 12 – ***Chronic dacryocystitis. Mucous metaplasia of the lining epithelium with one invagination that protruded into its lamina propria, which was infiltrated by inflammatory cells (HE staining, ×200).***

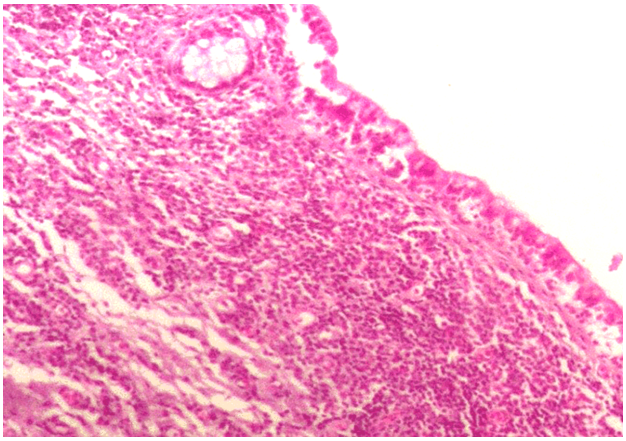

Figure 13 – ***Chronic dacryocystitis. Invagination of mucous metaplastic epithelium into the lamina propria produced histopathological features similar to Henle's glands (HE staining, ×100).***

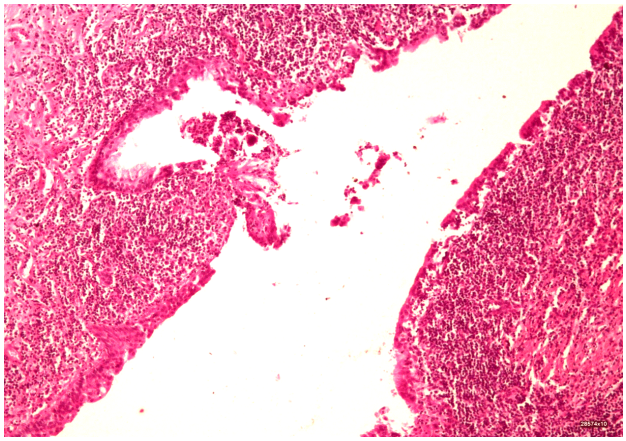

Figure 14 – ***Chronic dacryocystitis. The lining epithelium transformed into squamous epithelium (squamous metaplasia) (HE staining, ×200).***

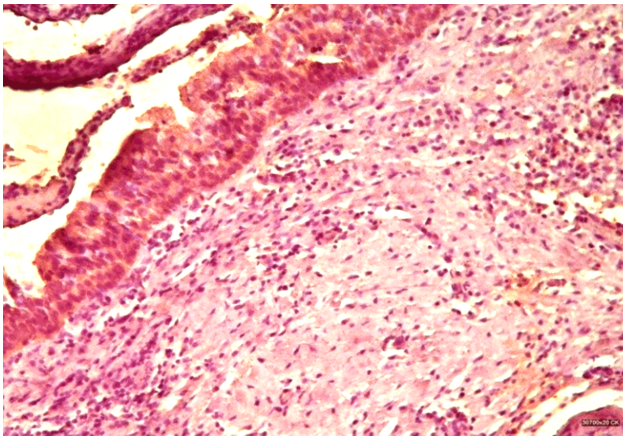

Figure 15 – ***Chronic dacryocystitis. Squamous metaplasia of the lining epithelium could be demonstrated due to its immunopositivity for CK AE1/AE3 (Immunostaining, anti-CK AE1/AE3 antibody, ×200).***

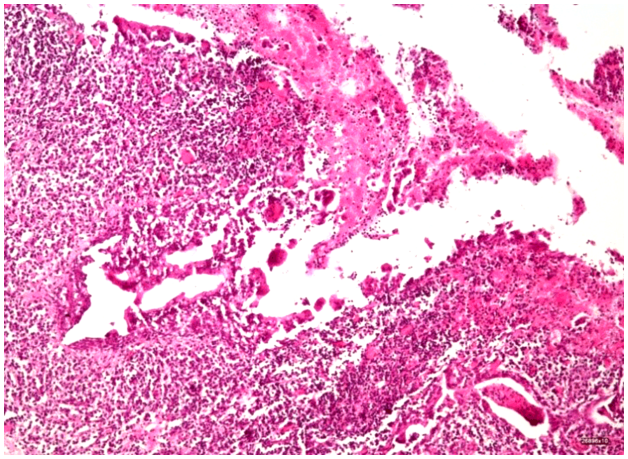

Figure 16 – *Chronic dacryocystitis. The lacrimal sac wall presented in many places necrosis with denudation of the lining epithelium. The detached cells could be found into its lumen, along with inflammatory cells. The lamina propria showed moderate inflammatory cell infiltration and many newly formed capillary vessels (HE staining, ×100).*

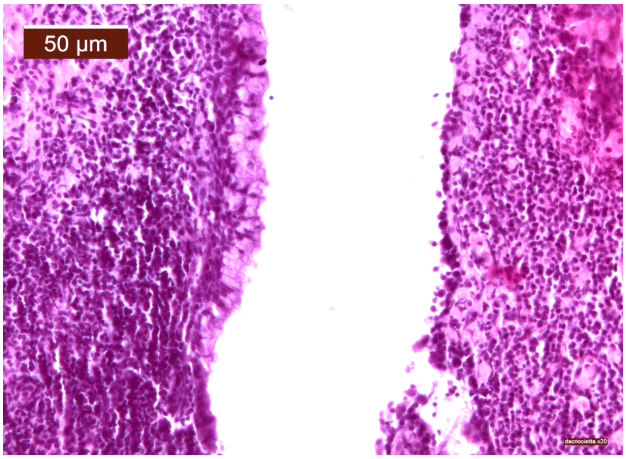

Figure 17 – *Chronic dacryocystitis. One of the lacrimal sac wall showed mucous metaplasia, the other one presented necrosis and denudation of its lining epithelium. On the left side there were severe inflammatory cell infiltration, but on the right side there were only a moderate inflammatory cell infiltration, but a severe capillary proliferation (HE staining, ×200).*

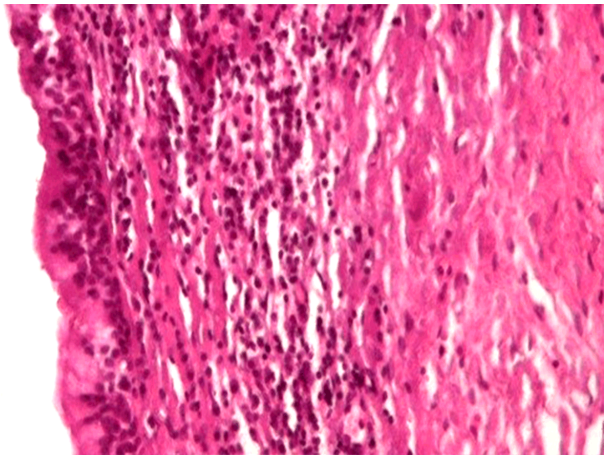

Figure 18 – *Chronic dacryocystitis. Mild inflammation (HE staining, ×400).*

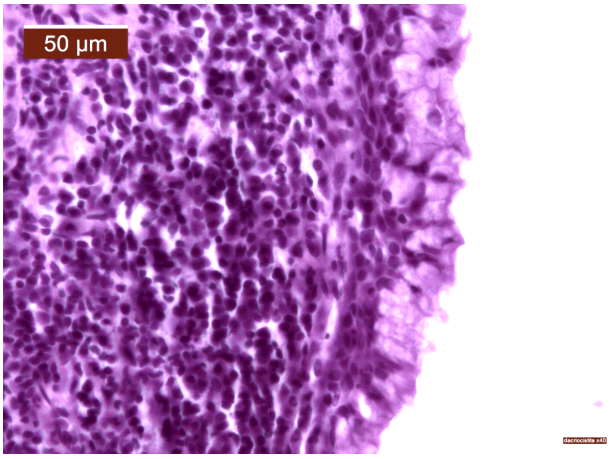

Figure 19 – *Chronic dacryocystitis. Severe infiltration of lamina propria with lymphocytes (HE staining, ×400).*

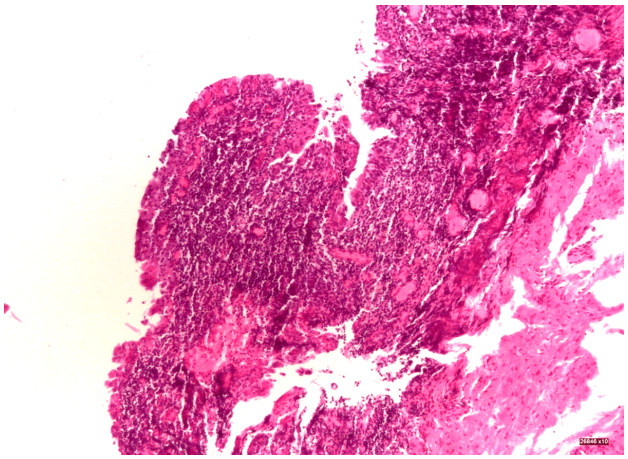

Figure 20 – *Chronic dacryocystitis. Papillary infolding of lacrimal sac wall due to the presence of heavy inflammatory cell infiltration and severe proliferation of thin-walled blood vessels into the lamina propria (HE staining, ×100).*

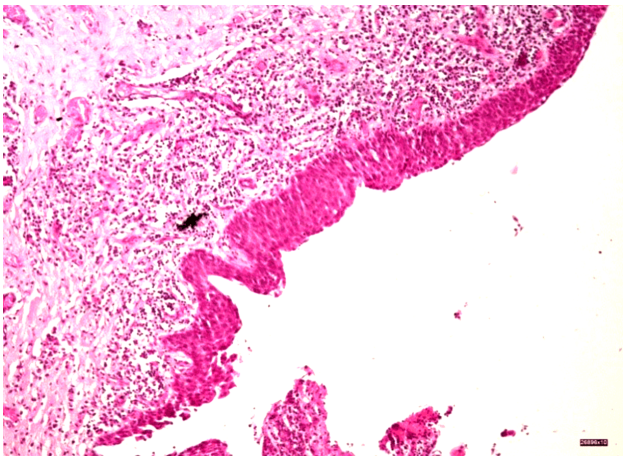

Figure 21 – *Chronic dacryocystitis. Below the lining epithelium that suffered squamous metaplasia could be seen a mild inflammatory infiltration and severe proliferation of capillary vessels (HE staining, ×200).*

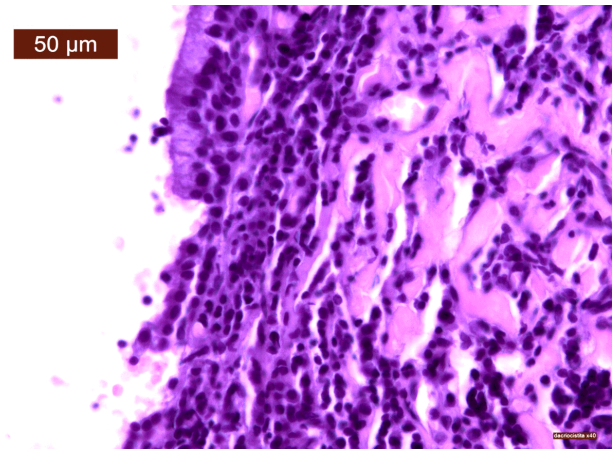

Figure 22 – ***Chronic dacryocystitis. Below the denuded or intact epithelium, among the inflammatory cells, there were thick collagen fibers occupying more than 50% of a HPF (HE staining, ×400).***

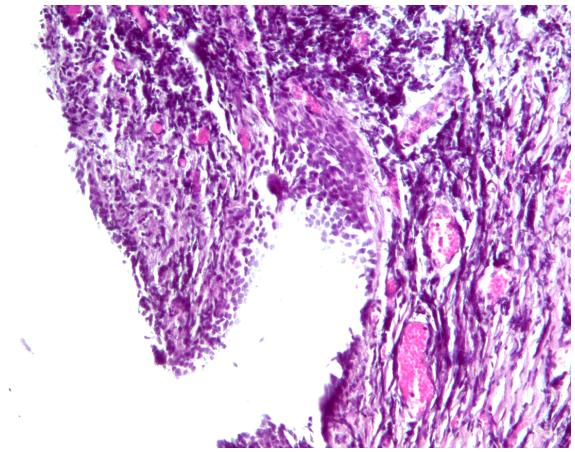

Figure 23 – ***Chronic dacryocystitis. The lining epithelium showed hyperplasia and the lamina propria revealed diffuse infiltration with lymphocytes, numerous capillary vessels, and a severe amount of fibrosis (HE staining, ×200).***

Table 1 – ***Gradation of histopathological features discovered in lamina propria of lacrimal sac wall***

Intensity of histopathological features	Inflammatory cell infiltrate (*n*=18 cases)	Fibrosis (*n*=18 cases)	Capillary proliferation (*n*=18 cases)
Mild (=1)	3 (16.66%)	11 (61.11%)	5 (27.77%)
Moderate (=2)	5 (27.77%)	5 (27.77%)	11 (61.11%)
Severe (=3)	10 (55.55%)	2 (11.11%)	2 (11.11%)

Table 2 – ***Dacryocystitis cases distribution based on chronic inflammation score***

Chronic inflammation score (CIS)	No. of cases (%)
Mild (<3)	1 (5.55%)
Moderate (3<CIS<6)	13 (72.22%)
Severe (>6)	4 (22.22%)

Discussion

The number of specimens with CD sent to the Department of Pathology over a 16-year period was quite small (less than 3%), but in line with its epidemiology [1]. We also found that in the region of Moldavia, Romania, over the last 16 years, CD began to grow annually, though non-systematized, as a group of senior patients living in poor conditions appeared in recent years.

In a significant study conducted in Denmark over a period of 90 years on 643 biopsies of lacrimal drainage system, Marthin *et al.* (2005) found that the incidence of CD in women was about twice as high than in male patients. The authors also found a significant difference between the two genders related to the average age of diagnosis of a CD, *i.e.*, 63.6 years in females, and 57.8 years in males [5]. In our study, we noticed that the disease affected aged women, mainly in their eighth and ninth decades of life. Marthin *et al.* (2005) also reported a higher incidence in aged people [5], but none of their patients were in the late decades of life as in our study.

In Nepal, Badhu *et al.* (2005) reported that CD occurred twice more frequent in premenopausal women. In this study, the average age was low, as the patients included in the study were in their third to fifth decades of life, facts that were correlated with environmental particularities of their country, respectively a subtropical climate with monsoons [7].

Ramesh Murthy (2011) states that CD is more common in adults over the age of 40, while the disease affects especially women with a peak age of 60–70 years [8]. There are also authors who suggested that women are five times more frequently affected than men probably due to narrower lacrimal ducts or use of irritative components in cosmetics [2].

In our study, we identified a greater incidence of CD on the left than on the right side, an aspect which was highlighted by other authors as well. Ramesh Murthy believes that this is probably because the nasolacrimal duct and the lacrimal fossa form a greater angle on the right than on the left side [8].

Histopathological features of CD have been investigated since the beginning of the 20th century. The Canadian ophtalmologist Samuel Hanford McKee, who was enrolled in the Canadian Army in the First World War to treat wounded soldiers, published in 1925 the first article about the histopathological features of CD. He showed that the lumen of the lacrimal sac was irregular and often narrowed due to inflammatory protuberances, which gave the surface of the mucosa a villous aspect [9]. These "finger-like" projections were considered to be the result of the granulation tissue and marked lymphocytic infiltration in the lamina propria. Lacrimal sac epithelium was thickened due to polystratification, caliciform cell formation, invaginations similar to Henle's glands, or was partially or completely denuded in some other areas [9]. Similar to our study, this author also found that the same case could present different histological features along the wall of the same inflamed lacrimal sac. It is interesting however that in the eight cases he presented, he did not report squamous metaplasia of the epithelium, which we have seen in almost a quarter of cases. This feature appeared only in one article published in 1958 by Prasad *et al.*, probably because, after the 1940, antibiotics were introduced into the ophthalmic medical practice for the treatment of this condition; surgical excision was thus performed after a longer evolution of the disease or perhaps some microorganisms with resistance to antibiotics appeared over time [10].

In our study, we have identified histological features of the lacrimal sac in CD as Prasad *et al.* did; however, we did not find any calcifications or bone formations in the wall of the lacrimal sac as these authors reported due to the fact that our patients sought the ophthalmologist's attention sooner, thus the course of the disease was shorter and these degenerative changes did not develop.

Despite the fact that new methods of diagnosis and conservative and surgical treatment for CD developed in 21st century, and the patients seek medical attention earlier than they used to do in the last century, the histological features of this disease changed to a small extent as it was dominated by characteristic epithelial changes and chronic inflammation in the sac wall. In our study, the pathologic features of the lining epithelium consisted of hyperplasia with eight to ten layers forming "finger-like" projections into the sac lumen, an excess of goblet cells formation that invaginated into lamina propria similar to Henle's glands, and incomplete or complete denudation of the mucosa, but these histopathological changes were also reported by some other researchers [1, 3, 9, 11].

Regarding the pathogenesis of the disease, some authors presumed that intraluminal exudate could be responsible for epithelial necrosis and for squamous metaplasia of the remaining epithelium due to chronic irritation [12]. The intraluminal content irritation upon the epithelial lining of the lacrimal sac can determine adaptive mechanisms that may lead to the substitution of epithelial cells that are sensitive to stress by squamous cells, which are capable to withstand an adverse environment. Therefore, the transformation of columnar to non-keratinized stratified squamous epithelium (squamous metaplasia) appeared in the lacrimal sac epithelium in response to chronic irritation due to inflammation; however, even if metaplasia is not directly carcinogenetic, the predisposing factors for metaplasia, if persistent, may induce malignant transformation in metaplastic epithelium. Therefore, more cases of malignant disease at the level of the lacrimal sac could develop if patients do not seek the attention of the ophtalmologist earlier in the course of their CD and also in the case of other ocular diseases with periocular and orbital implications [13].

However, other authors agree that lacrimal sac specimens most commonly show the presence of inflammation in a ratio from 79% to 98% of the cases [5, 11]. Non-granulomatous inflammation could be identified in most cases (85.1%), while granulomatous inflammation (sarcoidosis) was reported only in 2.1% of the cases [3]. In our study, we identified only non-specific chronic inflammation.

Chakrabarti *et al.* (2016) recommended to the ophthalmologists to perform biopsies of the lacrimal sac wall and advised pathologists to include the chronic inflammation score in the histological evaluation of specimens obtained by dacryocystectomies. Since a greater degree of inflammation is associated with a poor outcome, this score would help clinicians to monitor the dose and duration of therapy with anti-inflammatory drugs thereby modifying the course of the disease [1].

Amin *et al.* (2013) calculated chronic inflammation scores in all cases of their investigated CD and found moderate score in 82%, severe in 12% and mild in 6% cases [6]. In our case series, we also found a moderate chronic inflammation score in almost three quarters of cases but a significant number of cases (22.22%) also showed severe CIS. These percentages mean that the prognosis of these patients could be worse as unsuccessful results after dacryocystectomy could appear. Moreover, many authors reveal the fact that pathologists should identify inflammatory changes in a CD and at the same time should establish the CIS as these scores are important in treatment [1, 14]. On the other hand, the presence of severe lymphocytic infiltration, vascular proliferation, and fibrosis signify late stages of the disease.

As interleukin (IL)-8 expression can be found on the level of inflammatory cells, endothelial cell and fibroblasts, some authors highlighted its importance in inflammation [15, 16]. Along with them, we suggest this investigation be conducted in CD in order to obtain some new insights into this disease especially because more and more authors emphasize the relevance of lacrimal sac biopsies and their histopathological examination in all cases of dacryocystitis [3].

CD develop secondary to blocking the nasolacrimal duct and over-infecting it with Gram-positive and Gram-negative bacteria, among which Bharathi *et al.* isolated coagulase-negative staphylococci (CoNS) (44.2%), *Staphylococcus aureus* (10.8%), and *Streptococcus pneumoniae* (10%) [17]. Therefore, CD can be treated with an initial course of broad-spectrum oral antibiotics followed by external dacryocystorhinostomy or dacryocystectomy. However, a group of Romanian researchers [18] presented a novel nano-modified coating for wound dressings based on functionalized zinc oxide nanostructures and orange oil (ZnO@OO), which has an antimicrobial activity superior to bare ZnO nanoparticles (NPs) and to the control antibiotic against *S. aureus* and *Escherichia coli* as revealed by the lower minimal inhibitory concentration values.

Anyway, the treatment is important but more important is the presentation of the patient with CD as soon as possible to the ophthalmologist.

Conclusions

Histological specimens of chronic dacryocystitis are not usually found in the practice of pathology, but when examined, they reflect a multitude of features that ought to be taken into consideration as they could guide the ophthalmologists in their own practice. In our region, CD is frequent in elderly women, in their 8th or 9th decades of life, probably due to their deficient immune system, but also due to poor hygiene caused by poor living conditions. The histological appearances varied from patient to patient and even at the same patient varied from one area to another. There were histopathological changes indicating some adaptive changes, which could lead to the development of some malignant tumors at this level. Therefore, there is a need for education of patients with CD both in terms of ophthalmic hygiene and possible complications in the absence of a regular presentation to the ophthalmologist and a correct application of conservative treatment.

Conflict of interests

The authors do not have a financial interest/arrangement

or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of the manuscript.

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