Clinical significance of routine lacrimal sac biopsy during dacryocystorhinostomy: A comprehensive review of literature

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ABSTRACT

The main purpose of this paper is to provide the information about the incidence and types of pathology of secondary acquired obstructions of the lacrimal excretory outflow system caused by primary lacrimal sac non-neoplastic and neoplastic lesions. After a thorough literature search, 17 case-control studies were found and selected, data were extracted and categorized, to evaluate specific lacrimal sac pathology mimicking inflammation. A total of 3865 histopathologically examined lacrimal sac wall biopsy specimens from 3662 patients, taken during dacryocystorhinostomy for clinically presumed primary chronic dacryocystitis, were analyzed. The most common reported histopathological finding was non-specific chronic inflammation with or without fibrosis (94.15% of cases). Lacrimal sac-specific pathologies were present in 226 (5.85%) cases. Unsuspected lacrimal sac-specific pathologies were present in 55/226 (24.34%) cases. Almost 45% of primary lacrimal sac malignant neoplasms were not suspected, preoperatively and intraoperatively. Tumor-like lesions of the lacrimal sac were the most common pathology found: (1) lacrimal stones-dacryoliths, (2) pyogenic granuloma, (3) granulation tissues, (4) reactive lymphoid hyperplasia, and (5) lacrimal sac-specific inflammation (Wegener's granulomatosis and sarcoidosis). Neoplastic pathology was found in 55/3865 (1.42%) lacrimal sac wall biopsy specimens; of those, malignant cases were 2.24 times more frequent than benign. Lymphoma was the most common preoperatively unsuspected or intraoperatively unexpected neoplastic pathology. This analysis of the relevant literature highlights the value of routine lacrimal sac biopsy during surgery for clinically presumed primary acquired nasolacrimal duct obstruction.

KEY WORDS: Lacrimal sac; histopathology; specific pathology; chronic dacryocystitis; dacryocystorhinostomy
DOI: http://dx.doi.org/10.17305/bjbms.2016.1424 *Bosn J Basic Med Sci. 2017;17(1):1-8. © 2017 ABMSFBIH*

INTRODUCTION

Disorders of the lacrimal drainage system causing epiphora are a common problem in ophthalmology and, in the vast majority of cases, are primary or secondary acquired disorders. They occur in adulthood and are caused by non-specific pathology [1-3]. Idiopathic chronic inflammation, with or without fibrosis, occurs in clinically presumed primary acquired nasolacrimal duct obstruction (PANDO) [4-21]. A wide variety of causes, such as specific inflammatory [9-13], traumatic, mechanical, or neoplastic [14-18] may mimic idiopathic inflammation [19-21] in secondary acquired lacrimal drainage system obstruction (SALDO). Neoplastic causes are of special clinical interest (Figure 1) [22-26].

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Submitted: 22 May 2016/Accepted: 23 July 2016

In this review we investigate the prevalence and characteristics of specific primary lacrimal sac-pathology as a cause of SALDO. We conducted a comprehensive analysis of relevant published literature in which incisional biopsies of the lacrimal sac wall, obtained during surgery for clinically presumed PANDO, were performed and histopathologically analyzed.

MATERIALS AND METHODS

Literature search

Two researchers searched the literature independently and collectively participated in the study selection. MEDLINE (with both Ovid and PubMed), Embase, MD Consult, the Web of Science, and Google were searched to identify articles examining histopathological findings in specimens taken from the lacrimal sac wall at dacryocystorhinostomy (DCR) for presumed PANDO. The following keywords were used: Lacrimal sac, lacrimal sac histopathology, lacrimal sac specific pathology,

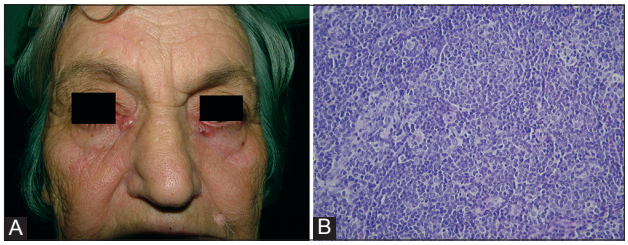

FIGURE 1. (A) A 75-year-old women with bilateral enlarged lacrimal sacs lasting for 28 months, and causing bilateral epiphora which, after synchronous bilateral dacryocystorhinostomy and incisional biopsy of the lacrimal sac wall, was given diagnosis of bilateral lacrimal sac lymphoma. (B) Lacrimal gland extranodal marginal zone B-cell non-Hodgkin lymphoma of mucosa-associated lymphoid tissue type (Periodic-acid Schiff [PAS] stain, 400x).

lacrimal sac biopsy, chronic dacryocystitis, and dacryocystorhinostomy. An attempt to contact all leading authors via email was made in an effort to find unpublished data.

Eligibility criteria

The inclusion and exclusion criteria were kept broad to maximize the sample size, and to include as much as possible original observational studies that had examined lacrimal sac specimens obtained during routine DCR, by means of histopathology. Disagreements were resolved through consensus.

Data extraction

After a thorough literature search, 17 case-control studies [4-21] were selected, reporting the results of histopathological examination of specimens taken from the lacrimal sac wall at DCR, for clinically presumed primary chronic dacryocystitis. The data were extracted and categorized to analyze the most common specific lacrimal sac pathology that masquerade as inflammation. A total number of 3865 lacrimal sac biopsy specimens from 3662 patients were analyzed.

Outcome definition

Two researchers classified independently the data into following categories:(1) Lacrimal sac biopsy specimens/patients; (2) Pathology other than chronic inflammation (with or without fibrosis) or normal-appearing mucosa, revealed by histopathology, i.e. specific pathology; (3) Primary benign lacrimal sac neoplasm revealed by histopathology; (4) Primary malignant lacrimal sac neoplasm revealed by histopathology; (5) Preoperatively suspected specific lacrimal sac pathology later confirmed by histopathology; (6) Preoperatively suspected primary malignant lacrimal sac neoplasm later confirmed by histopathology; (7) Preoperatively unsuspected but intraoperatively, inadvertently found specific lacrimal sac pathology; (8) Preoperatively unsuspected but intraoperatively, inadvertently found primary malignant lacrimal sac neoplasm; (9) Preoperatively and intraoperatively unsuspected specific lacrimal sac pathology revealed later by histopathology; and (10) Preoperatively and intraoperatively unsuspected primary malignant lacrimal sac neoplasm revealed by histopathology.

RESULTS

The most common reported histopathological finding was non-specific chronic inflammation with or without fibrosis (94.15% of the cases), confirming the diagnosis of primary process. Lacrimal sac specific pathologies were present in 226/3865 (5.85%) cases; this number varied between 0 and 27.42% in different studies (Tables 1 and 2; Supplemental Tables 1 and 2). Clinically and during surgery, unsuspected specific pathologies were present in 55/226 (24.34%) cases; this number varied between 0 and 11.82% in different studies (in 5/17 studies [29.41%] it is not stated [or not available] so the number of clinically and intraoperatively unrecognized cases may be even higher) (Supplemental Table 3).

Among lacrimal sac-specific pathology, tumor-like lesions (granulation tissues, pyogenic granuloma, reactive lymphoid hyperplasia, and cases of lacrimal sac-specific inflammation such as Wegener's granulomatosis and sarcoidosis) and lacrimal stones (dacryoliths) were the most common disorders (Supplemental Table 4). Neoplastic pathology was found in 55/3865 (1.42%) lacrimal sac wall biopsy specimens; of those, malignant were 2.24 times more frequent than benign cases (Supplemental Tables 2 and 5). However, the percentage of neoplastic pathology out of the overall specific pathology (226 cases) found in the lacrimal sac wall biopsy specimens was much higher, 24.34% (Supplemental Tables 2 and 5). Primary benign lacrimal sac neoplasms revealed by histopathology were noted in 17/3865 (0.44%) cases; this number varied between 0 and 1.61% in different studies (Supplemental Tables 2 and 5). Primary malignant lacrimal sac pathology was present in 38/3865 (0.98%) cases; this number varied between 0 and 3.45% in different studies, and lymphoma was the most common entity reported (Supplemental Tables 2 and 5). Preoperatively suspected specific lacrimal sac pathology, and later confirmed by histopathology, was present in 25/3865 (0.65%) cases; this number varied between 0 and 3.71% in different studies (Supplemental Table 3). These pathological cases were suspected because of known preoperative history or evidence of relevant local or systemic conditions which could be anticipated to involve the lacrimal drainage system. Preoperatively suspected primary malignant lacrimal sac neoplasm, later confirmed by histopathology, was present in 7/3865 (0.18%) cases; this number varied between 0 and 1.59% in different studies (Supplemental Table 3). Pre- or intraoperatively unsuspected malignancies were present in 17/3865 (0.44%) cases; this number varied between 0 and 1.61% in different studies (Supplemental Table 3).

TABLE 1. Seventeen case-control studies reporting lacrimal sac wall specific pathology in cases of clinically presumed primary chronic dacryocystitis

Reference	Lacrimal sac biopsy		Lacrimal sac specific pathology	
	Specimens (n)	Patients (n)	n	%
Mauriello et al. (1992)[4]	44	44	0	0
Tucker et al. (1997)[5]	162	150[B]	9	5.55
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7]	224	NA	NA	
Çiftci et al. (2005)[8]	23	23[F]	4	17.39
Lee-Wing and Ashenhurst (2001)[9]	202	166	12	5.94
DeAngelis et al. (2001)[10]	104	100	13	12.50
Bernardini et al. (2002)[11]	302	258[D]	17	5.63
Yazici et al. (2002)[12]	90	NA	NA	
Soparkar and Patrinely (2003)[13]	220	220[E]	26[A]	11.82
Anderson et al. (2003)[14]	377	316	69	18.30
Merkonidis et al. (2005)[15]	193	164[C]	3	1.55
Özgur et al. (2008)[16]	62	59	17	27.42
Kashkouli et al. (2010)[17]	87	87	0	0
Heindl et al. (2010)[18]	500	474	19	3.80
Altan-Yaycioglu et al. (2010)[19]	205	205	4	1.95
Salour et al. (2010)[20]	471	449	12	2.55
Knežević et al. (2012)[21]	599	543	21	3.51
Total	3865	3662	226	5.85

NA: Full paper was not available, only abstract; [A]not precisely stated; [B]endoscopic DCR performed in 16 of 150 patients; [C]endoscopic DCR performed in all patients; [D]patients having signs or symptoms suggestive of lacrimal sac tumor were excluded from the study; [E]patients in which infiltrative or neoplastic disease was strongly suspected preoperatively or intraoperatively, and patients with obvious traumatic cause were excluded; Fpatients with previously failed DCR; DCR: dacryocystorhinostomy

TABLE 2. Overall review of lacrimal sac specific pathology, from a clinical point of view

Lacrimal sac specific pathology	n (%)
Preoperatively suspected	25 (11.06)
Preoperatively unsuspected but inadvertently found intraoperatively	102 (45.13)
Preoperatively and intraoperatively unsuspected	55 (24.34)
Not stated in the text of the article	44 (19.47)
Total	226

The evidence of intraoperatively found lacrimal sac abnormality (including dacryoliths) was noted in 102/3865 (2.64%) cases; this number varied between 0 and 17.39% in different studies (Supplemental Table 6). Preoperatively unsuspected but intraoperatively, inadvertently found primary malignant lacrimal sac neoplasm was noted in 14/3865 (0.36%) cases; this number varied in between 0 and 1.20% in different studies (Supplemental Table 6).

However, the percentage of unrecognized specific pathologies out of the total number of specific pathologies (226 cases), found among the lacrimal sac wall biopsy specimens, was much higher, up to 24%. The percentage of unrecognized malignant neoplasms out of the total number of malignancies (38 cases) was even higher, up to 45% (Supplemental Table 3).

DISCUSSION

The main purpose of this paper is to provide information about the incidence and types of pathology of SALDO caused by primary lacrimal sac non-neoplastic and neoplastic lesions. This was accomplished by a diagnostic investigation of a pool of routine incisional biopsy samples of 3865 consecutive, clinically presumed primary dacryocystitis cases treated by DCR, from 17 clinicopathological studies [4-21]. The first and most cited study performed by Linberg and McCormick [3] was not included in this analysis because the biopsy specimens were obtained from the nasolacrimal duct and not from the lacrimal sac. The authors from the 17 studies had assessed indirectly an incidence of significant lacrimal sac pathology mimicking (or clinically suspected for) PANDO. This was accomplished by determining the incidence of lacrimal sac tumors found in routine biopsy material obtained from the sac during PANDO surgery. Most of the authors from the 17 studies indicated that only a selective lacrimal sac biopsy during DCR in atypical, clinical, or intraoperatively suspicious cases, rather than routine biopsy of all patients with PANDO, is warranted. According to these studies, routine biopsies are unnecessary [16,20,27], not indicated [15], expensive and burdensome [11], of questionable benefit [10], time-consuming, the rate of malignancies is low enough to justify not to perform the biopsy [16], etc. In their opinion, specific pathology is a rare finding in clinically presumed PANDO. Thus, biopsy is justified only in the following cases: (1) if any suspicion of abnormality of the lacrimal sac exists, (2) in those cases with a positive history of systemic disease, or (3) when there is a suspicion of a neoplasm based on the clinical, historical, or intraoperative findings. However, as our analysis has undoubtedly revealed, a significant number of other specific pathological processes may arise in the lacrimal sac and masquerade

as chronic inflammation. There is always a risk of overlooking primary malignant pathologies originated in the lacrimal sac causing a nasolacrimal system obstruction. Malignant neoplasia, especially lymphoproliferative neoplasia, can easily be overlooked [28-32]. According to our results, almost 45% of primary lacrimal sac malignant neoplasms were unsuspected, preoperatively and intraoperatively, emphasizing the importance of adequate early diagnosis.

Clinically, it is sometimes very difficult to differentiate chronic dacryocystitis from lacrimal sac neoplasm, especially in the early phase (stage 1, according to Ni et al. [23]), when there is an absence of definite tumor on palpation. Furthermore, intraoperatively, any gross abnormality of the lacrimal sac may not be visible. Moreover, there is no absolute guarantee that intraoperative normal appearance of the lacrimal sac indicates that there is no pathologic process in the sac other than chronic inflammation or fibrosis. Experienced surgeons were up to 98% sensitive in detecting specific lacrimal sac pathology [21]. Nevertheless, malignant neoplasia, without clinical signs or symptoms suggestive of a possible underlying lacrimal sac tumor, and incipient to produce a grossly visible abnormality, could appear normal or consistent with chronic inflammation [33-39]. The value of routine histological examination of the lacrimal sac wall at DCR, in those cases, is indubitable. The pathologic diagnosis of malignant neoplastic process impacts further clinical management and prompts a systemic workup to determine whether additional therapy is required.

Obtaining a representative incisional biopsy sample of the lacrimal sac lesion is challenging especially in cases without any grossly visible pathology at the time of surgery. Sometimes, biopsy may yield a false negative result and a misdiagnosis of chronic inflammation can be made. Consequently, when one has to review or evaluate the results of blind/random incisional biopsies of the lacrimal sac wall, in order to estimate the risk of missing specific pathologies or to improve the detection rate of early tumors, those facts should be considered.

Dacryoliths, primary lacrimal sac lymphoma, sarcoidosis (in most of the cases with confirmed systemic disease), pyogenic granuloma, and granulation tissue are the most common specific lacrimal sac pathologies that one can expect in patients with clinically presumed PANDO. In our analysis, lymphoma was the most common malignant neoplasm found in the patients with presumed PANDO. Further, it was the most common preoperatively unsuspected or intraoperatively unexpected pathology present in the patients with presumed PANDO. At this moment, we can only hypothesize how sustained inflammation increases the risk of genotoxic insults and initiation of oncogenesis. Among epithelial neoplasms, the most common were Schneiderian papilloma (inverted and exophytic types) and squamous cell carcinoma.

CONCLUSION

This analysis highlights the value of routine lacrimal sac biopsy during DCR for clinically presumed PANDO. Routine incisional biopsy of the lacrimal sac wall during DCR does not affect the success of the surgery (if biopsy specimen is not too large to compromise the flap required for an adequate anastomosis to the nasal mucosa, in external DCR). It is certainly not a time-consuming procedure for an ophthalmologist surgeon and does not increase the costs of the surgery. In addition, the costs of histopathological evaluation are assuredly affordable even for low-income countries. This procedure may confirm a previously known diagnosis or, more importantly, may bring forward the diagnosis of unsuspected or unexpected neoplasia.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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SUPPLEMENTAL TABLES

SUPPLEMENTAL TABLE 1. Lacrimal sac biopsy specimens with specific non-neoplastic and neoplastic pathology

Reference	n		
	Lacrimal sac biopsy specimens with specific pathology	Non-neoplastic specific pathology	Neoplastic specific pathology
Mauriello et al. (1992)[4]	0		0
Tucker et al. (1997)[5]	9	7	2
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7]	NA	NA	NA
Çiftci et al. (2005)[8]	4	4	0
Lee-Wing and Ashenhurst (2001)[9]	12	12	0
DeAngelis et al. (2001)[10]	13	13	0
Bernardini et al. (2002)[11]	17	11	6
Yazici et al. (2002)[12]	NA	NA	NA
Soparkar and Patrinely (2003)[13]	26*	21*	5*
Anderson et al. (2003)[14]	69	50	19
Merkonidis et al. (2005)[15]	3	2	1
Özgur et al. (2008)[16]	17	15	2
Kashkouli et al. (2010)[17]	0	0	0
Heindl et al. (2010)[18]	19	11	8
Altan-Yaycioglu et al. (2010)[19]	4	2	2
Salour et al. (2010)[20]	12	10	2
Knežević et al. (2012)[21]	21	13	8
Total	226	171	55

NA: Paper was not available; *not precisely stated in numbers but diagnoses included sarcoidosis, tissue-infiltrating fungal disease, a case of "vasculitis", leukemia, lymphoma, fibrous histiocytoma, solitary fibrous tumor, and squamous cell carcinoma ***in situ***

SUPPLEMENTAL TABLE 2. Primary neoplastic pathology revealed by histopathology

Reference	Primary benign lacrimal sac neoplasm revealed by histopathology		Primary malignant lacrimal sac neoplasm revealed by histopathology	
	n	%	n	%
Mauriello et al. (1992)[4]	0		0	
Tucker et al. (1997)[5]	1	0.62	1	0.62
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7]	NS		NS	
Çiftci et al. (2005)[8]	0	0	0	0
Lee-Wing and Ashenhurst (2001)[9]	0	0	0	0
DeAngelis et al. (2001)[10]	0	0	0	0
Bernardini et al. (2002)[11]	3	0.99	3	0.99
Yazici et al. (2002)[12]	NS		NS	
Soparkar and Patrinely (2003)[13]	2*	0.91*	3*	1.36*
Anderson et al. (2003)[14]	6	1.59	13	3.45
Merkonidis et al. (2005)[15]	1	0.52	0	0
Özgur et al. (2008)[16]	1	1.61	1	1.61
Kashkouli et al. (2010)[17]	0	0	0	0
Heindl et al. (2010)[18]	1	0.20	7	1.40
Altan-Yaycioglu et al. (2010)[19]	0	0	2	0.98
Salour et al. (2010)[20]	0	0	2	0.42
Knežević et al. (2012)[21]	2	0.33	6	1.00
Total	17**	0.44	38**	0.98
% out of specific lacrimal sac pathology (226)		7.52**		16.81**
% of primary lacrimal sac neoplasms out of total number of lacrimal sac specimens (3865)		1.42**		
% of primary lacrimal sac neoplasms out of specific lacrimal sac pathology (226)		24.34**		

NS: Not stated; *not precisely stated; **including Soparkar and Patrinely[13] cases

SUPPLEMENTAL TABLE 3. Preoperatively suspected, and preoperatively and intraoperatively unsuspected lacrimal sac pathology, especially malignant neoplastic cases

Reference	Preoperatively suspected and later confirmed by histopathology				Preoperatively and intraoperatively unsuspected but later revealed by histopathology			
	Lacrimal sac specific pathology		Lacrimal sac primary malignant neoplasm		Lacrimal sac specific pathology		Lacrimal sac primary malignant neoplasm	
	n	%	n	%	n	%	n	%
Mauriello et al. (1992)[4]	0		0		0		0	
Tucker et al. (1997)[5]	0	0	0	0	3	1.85	1	0.62
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7]	NS		NS		NS		NS	
Çiftci et al. (2005)[8]	0	0	0	0	0	0	0	0
Lee-Wing and Ashenhurst (2001)[9]	0	0	0	0	NS		NS	
DeAngelis et al. (2001)[10]	NS	NS	NS	NS	NS		NS	
Bernardini et al. (2002)[11]	6	1.99	6	1.99	3	0.99	0	0
Yazici et al. (2002)[12]	NS		NS		NS		NS	
Soparkar and Patrinely (2003)[13]	0	0	0	0	26*	11.82*	3*	1.36*
Anderson et al. (2003)[14]	14	3.71	12	3.18	10	2.65	4	1.06
Merkonidis et al. (2005)[15]	0	0	0	0	2	1.04		
Özgur et al. (2008)[16]	2	3.23	2	3.23	0	0	1	1.61
Kashkouli et al. (2010)[17]	0	0	0	0	0	0	0	0
Heindl et al. (2010)[18]	1	0.20	1	0.20	0	0	0	0
Altan-Yaycioglu et al. (2010)[19]	0	0	0	0	1	0.49	1	0.49
Salour et al. (2010)[20]	2	0.42	0	0	1	0.21	1	0.21
Knežević et al. (2012)[21]	0	0	0	0	9	1.50	6	1.00
Total	25		21		55**		17**	
% out of total number of lacrimal sac specimens (3865)		0.65		0.54		1.42		0.44
% out of specific lacrimal sac pathology (226)		11.06				24.34		
% out of primary malignant lacrimal sac pathology (38)				18.42				44.74**

NS: Not stated; *not precisely stated; **including Soparkar and Patrinely[13] cases

SUPPLEMENTAL TABLE 4. Lacrimal sac biopsy specimens with specific non-neoplastic pathology

Reference	Lacrimal sac biopsy specimens with specific non-neoplastic pathology											
	Lacrimal stones (dacryoliths)		Specific inflammation		Granulation tissue		Pyogenic granuloma		Reactive lymphoid hyperplasia		Other	
	n	%	n	%	n	%	n	%	n	%	n	%
Mauriello et al. (1992)[4]												
Tucker et al. (1997)[5]	6	66.67	1	11.11								
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7]					0	0	0	0				
Çiftci et al. (2005)[8]					3	75	1	25				
Lee-Wing and Ashenhurst (2001)[9]	8	66.66			1	8.33	1	8.33	2	16.67		
DeAngelis et al. (2001)[10]	9	69.23	4	30.77								
Bernardini et al. (2002)[11]	6	35.29	4	23.53			1	5.88				
Yazici et al. (2002)[12]												
Soparkar and Patrinely (2003)[13]*			*	*								
Anderson et al. (2003)[14]	29	42.03	14	20.29	2	2.90	1	1.45	4	5.80		
Merkonidis et al. (2005)[15]			2	66.67								
Özgur et al. (2008)[16]					9	52.92	2	11.78			4	
Kashkouli et al. (2010)[17]												
Heindl et al. (2010)[18]			7	36.82			4	21.07				
Altan-Yaycioglu et al. (2010)[19]			1	25					1	25		
Salour et al. (2010)[20]					9	75			1	8.33		
Knežević et al. (2012)[21]	7	33.34	2	9.52	2	9.52	1	4.76	1	4.76		
Total (out of 226)	65	28.76	>35 (56)	>15.49 (24.78)	26	11.50	11	4.87	9	3.98	4	1.77

*Not precisely stated in numbers but diagnoses included sarcoidosis, tissue-infiltrating fungal disease, and a case of "vasculitis"

SUPPLEMENTAL TABLE 5. Lacrimal sac biopsy specimens with primary neoplastic pathology

Reference	Lacrimal sac biopsy specimens with specific pathology					
	Primary neoplastic benign		Primary neoplastic malignant			
			Lymphomas		Epithelial neoplasms	
	n	%	n	%	n	%
Mauriello et al. (1992)[4]						
Tucker et al. (1997)[5]	1	11.11	1	11.11		
Çiftci et al. (1999)[6] and Çiftci et al. (2000);[7] Çiftci et al. (2005)[8]						
Lee-Wing and Ashenhurst (2001)[9]	2	16.67				
DeAngelis et al. (2001)[10]						
Bernardini et al. (2002)[11]	3	17.65	3	17.65		
Yazici et al. (2002)[12]						
Soparkar and Patrinely (2003)[13]*	*		*		*	
Anderson et al. (2003)[14]	5	7.24	9	13.05	5	7.24
Merkonidis et al. (2005)[15]			1	33.33		
Özgur et al. (2008)[16]	2	11.78	1	5.88		
Kashkouli et al. (2010)[17]						
Heindl et al. (2010)[18]	1	5.26	3	15.78	4	21.07
Altan-Yaycioglu et al. (2010)[19]			1	25	1	25
Salour et al. (2010)[20]			2	16.67		
Knežević et al. (2012)[21]	2	9.52	5	23.82	1	4.76
Total (out of 226)	>16	>7.08 (9.95)	>26	>11.50 (14.38)	>11	>4.87 (7.75)

*Not precisely stated in numbers but diagnoses included leukemia, lymphoma, fibrous histiocytoma, solitary fibrous tumor, and squamous cell carcinoma ***in situ***

SUPPLEMENTAL TABLE 6. Preoperatively unsuspected but intraoperatively, inadvertently found lacrimal sac pathology, especially malignant neoplastic cases

Reference	Preoperatively unsuspected but intraoperatively, inadvertently found			
	Lacrimal sac specific pathology		Lacrimal sac primary malignant neoplasm	
	n	%	n	%
Mauriello et al. (1992)[4]	0	0		
Tucker et al. (1997)[5]	6	3.70	0	0
Çiftci et al. (1999)[6] and Çiftci et al. (2000)[7];	NS		NS	
Çiftci et al. (2005)[8]	4	17.39	0	0
Lee-Wing and Ashenhurst (2001)[9]	4*	1.98*	0	0
DeAngelis et al. (2001)[10]	NS	NS	0	0
Bernardini et al. (2002)[11]	9	2.98	3	0.99
Yazici et al. (2002)[12]	NS		NS	
Soparkar and Patrinely (2003)[13]	0	0	0	0
Anderson et al. (2003)[14]	45	11.94	3	0.80
Merkonidis et al. (2005)[15]	1	0.52	0	0
Özgur et al. (2008)[16]	NS	NS	0	0
Kashkouli et al. (2010)[17]	0	0	0	0
Heindl et al. (2010)[18]	18	3.60	6	1.20
Altan-Yaycioglu et al. (2010)[19]	1	0.49	1	0.49
Salour et al. (2010)[20]	2	0.42	1	0.21
Knežević et al. (2012)[21]	12	2	0	0
Total	102		14	
% out of total number of lacrimal sac specimens (3865)		2.64		0.36
% out of specific lacrimal sac pathology (226)		45.13		
% out of primary malignant lacrimal sac pathology (38)				36.84

NS: Not stated; *not precisely stated