·Letter to the Editor·

Non-keratinising undifferentiated nasopharyngeal-type carcinoma of the lacrimal sac

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Dear Editor,

We present a case of non-keratinising undifferentiated nasopharyngeal-type carcinoma (UNPC) of nasolacrimal sac and review the previously reported cases and their treatment options and prognosis. Squamous cell carcinoma with a characteristic lymphoid stroma is a type of poorly differentiated carcinoma typically occurring in the nasopharynx [1]. Non-keratinising UNPC, so called lymphoepithelioma-like carcinoma (LELC), of the lacrimal sac has morphological features similar to the nasopharyngeal carcinoma but arises in locations outside of the nasopharynx, such as salivary gland, lung, stomach, thymus, skin, urinary bladder, uterine cervix and breast [2-5]. Before a diagnosis of UNPC in sites other than the nasopharynx can be made, a secondary tumour from a nasopharyngeal carcinoma must be ruled out [6]. UNPC is an extremely rare malignancy in the lacrimal drainage system with only 10 cases (in 9 publications) reported so far[6-14].

Case Report A 58 year-old Caucasian female presented with a two-year history of right sided epiphora, sticky eye discharge, and a swelling under the medial canthal tendon. Fluorescein dye disappearance was delayed on the affected side. The lacrimal apparatus syringing with 0.9% normal saline *via* lower lacrimal canaliculus resulted in regurgitation of the solution *via* upper lacrimal punctum indicating an anatomical naso-lacrimal duct obstruction. An otolaryngology examination including nasal endoscopy performed by ENT colleagues was unremarkable and she was offered right external dacryocystorhinostomy (DCR) to alleviate her symptoms.

During the external DCR procedure, when the lacrimal sac was opened a solid tumour confined to the right lacrimal sac was revealed. The lacrimal sac and the tumour were excised en bloc. Histopathological analysis confirmed the diagnosis of UNPC, so called LELC, of the lacrimal sac (Figures 1 and 2). Immunohistochemistry revealed tumour cell expression of cytokeratins AE1/AE3, 5/6, 14, 19 and CAM5.2. However, *in situ* hybridization for Epstein Barr virus (EBV) on this sample was negative.

Adjuvant treatment with radical radiotherapy (66 Gy in 33 fractions) over the lacrimal sac area and lymphatic drainage areas resulted in complete remission. As a result of radiation induced tissue damage she developed oral mucositis, periocular swelling and radiation keratopathy. Fortunately,

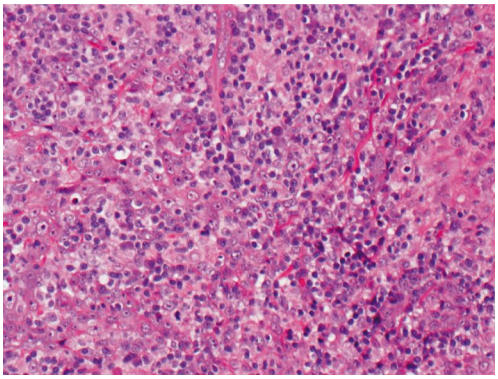

Figure 1 Large atypical tumour cells with vesiculated nuclei and prominent nucleoli and intervening scattered small lymphocytes.

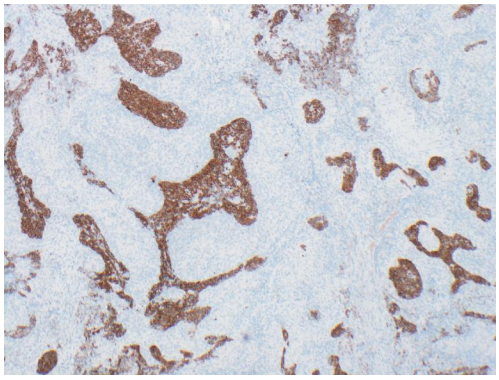

Figure 2 Immunohistochemistry for epithelial marker (AE1/AE3) highlighting the tumour cells in brown The extensive background lymphocytic infiltrate is negative.

Table 1 Patient demographics, clinical features, results of the investigations

Authors	Age/Gender	Race	Symptoms/signs of local, regional or systemic spread	Duration of symptoms prior to suspicion of a malignancy (mo)	EBV status	Imaging	Primary site	Immuno-histochemical investigations
Thalacker *et al* 1995[7](German)	59/F	-	MCL, E	18	-	CT/MRI: NLD mass extending into medial orbit	NLD	-
Leung *et al* 1996[8]	45/F	Chinese	Submandibular swelling, P (12mo later)	6	EBER+, Serum EBV VCA IgA+	CT: small soft tissue mass in LS (initially missed)	LS, IMO	-
Liu *et al* 2009[9]	82/M	Taiwanese	E (18mo), MCL, P, EXT	18	EBER+	CT: Left LS soft tissue mass	LS	Cytokeratin 5/6+ (tumour cells), CD3/20+ (stromal lymphoid cells)
Tam *et al* 2010[10]	61/F	Taiwanese	E, MCL, NO, R, Ex, tumour under the inferior turbinate	6	EBER+, ELMP-1+, Serum EBV VCA IgA+, EBV VCA IgA+, EBV EA+, EBV NA1 IgA+	MRI: NLD tumour extending into inferior meatus	NLD, maxillary bone	-
Low *et al* 2011[11]	55/M	Singapore	E, MCL	24	EBER+	MRI: Homogeneously enhancing lobulated mass arising from LS with orbital invasion	LS, NLD	Cytokeratin AE1/AE3+
Doi *et al* 2012[12]	49/F	Japanese	E, MCL, OT	1	-	MRI: Heterogeneously enhancing mass involving LS, Ethmoid sinus & orbit	LS	-
Qiu *et al* 2013[6]	20/F	Chinese	E, MCL	5	EBER+	CT: Homogenous, well-defined right lacrimal sac soft-tissue mass. No adjacent invasion	LS, IMO	Cytokeratin 19+, P63+
Qiu *et al* 2013[6]	53/F	Chinese	E, MCL, EOP	1	EBER+	CT: Heterogenous soft-tissue lacrimal sac mass with orbital/retrobulbar extension	LS, IMO	Keratin+
Keelawat *et al* 2015[13]	67/F	Thailand	E, MCL	1	EBER+	CT: Homogenously enhancing mass involving LS, medial orbit & lower eyelid	LS, LL, IR, MR	Epithelial membrane antigen+
Jakobiec *et al* 2015[14]	63/F	African-American	E, MCL	'Brief' duration (Misdiagnosed as dacryocystitis & DCR performed). Malignancy discovered 24mo later)	EBER-	CT (at presenatation): suspicious enlargement of NLD (initially missed) CT (2y later): Mass within enlarged R/NLD, LS & adjacent tissue invasion	NLD, LS	Cytokeratin AE1/AE3+, P63+, CD20/3+, T/B lymphocytes
Our case	58/F	Caucasian	E, MCL	24	EBER-	No indication for imaging pre-op	NLD, LS	Cytokeratin AE1/AE3+, Cytokeratin5/6/14/19+, Cytokeratin CAM 5.2+

E: Epiphora; EBER: EBV RNA in tumour cells; EBV VCA IgA: Serum IgA against EBV capsid antigen; EBV EA+NA1 IgA: Serum EBV early antigen and nuclear antigen-1; EOP: External ophthalmoplegia; Ex: Epistaxis; EXT: Exotropia; IMO: infero-medial orbit; LMP-1: EBV latent membrane protein-1 oncogene in tumour cells; LL: Lower lid, IR : Inferior rectus, MR: Medial rectus; LS: Nasolacrimal sac; MCL: Medial canthal lump; NLD: Nasolacrimal duct; NO: Nasal obstruction; OT: Orbital tumour; P: Proptosis; R: Rhinorrhea.

the oral mucositis was transient and the periocular swelling improved spontaneously. Subsequently she developed a radiation induced cataract, retinal neovascularisation which resulted in rubeotic glaucoma. The corneal ulceration responded well to topical and oral antibiotics and rubeotic glaucoma required pan-retinal photocoagulation, cyclodiode laser treatment in addition to the topical anti-glaucoma medication, steroids and mydriatics. Her visual acuity at her most recent follow up visit was "counting fingers" in the affected eye. So far she has been followed up for 30mo since diagnosis of UNPC and there is no evidence of local recurrence or distant metastasis. This study adhered to the tenets of the Declaration of Helsinki.

Review of the Literature A PubMed and MEDLINE searches for "undifferentiated nasopharyngeal-type carcinoma", "UNPC", "nasopharyngeal-type carcinoma", "lymphoepithelioma", "lymphoepithelial carcinoma", "lymphoepithelioma-like carcinomas (LELC)" were performed. All relevant publications and related articles were scrutinised for UNPC or LELC of the lacrimal drainage system. Eight articles in English and one in German language reported a total of 10 cases of non-keratinising UNPC of the lacrimal sac (Tables 1, 2). The article in German was translated into English language and the relevant details of this case were extracted.

Table 1 summarises the clinical signs and symptoms at

Table 2 Treatment options and prognosis

Authors	Local treatment	DFS (mo)	Loco-regional relapse/metastases	Treatment received for relapse	Response to treatment of recurrences	Adverse effects	FU since initial treatment (mo)	Further loco-regional relapse/metastases
Thalacker *et al* 1995[7](German)	LRx, Chemotherapy	30	None	N/A	N/A	None	30	N/A
Leung *et al* 1996[8]	DCT, LRx (50 Gy)	24	Ipsilateral Cervical LN	LRx (60 Gy) to head & neck	Complete remission	None	24	None
Liu *et al* 2009[9]	DCT, LRx (56 Gy)	6	Ipsilateral submandibular LN (diagnosed by FNAB)	Modified neck dissection, RTx, patient declined chemotherapy	Complete remission	None	12	None
Tam *et al* 2010[10]	Sx (en-bloc) with medial maxillectomy,LRx (64 Gy)	33	None	N/A	N/A	None	33	N/A
Low *et al* 2011[11]	Transcanalicular FNAB; Medial orbitectomy, maxillectomy (through lateral rhinotomy) with removal of puncta & canaliculi. LRx (66 Gy)	15	None	N/A	N/A	None	15	N/A
Doi *et al* 2012[12]	Sx (wide resection & orbital exenteration) with rectus abdominis musculocutaneous flap. LRx (60 Gy)	0	R/subaural, parotid, submandibular, deep cervical LN, R/parotid gland, R/lung	Extirpation of parotid tumour, Chemotherapy (Docetaxel, Cisplatin, 5-FU)	Poor	None	7	Mediastinal LN, Lung & skin metastasis. Died 7mo after the initial surgery
Qiu *et al* 2013[6]	DCT, Chemotherapy (docetaxel–cisplatin-5FU× 4cycles), LRx (68 Gy)	9	Inferomedial orbit (Ipsilateral), Orbit, nasolacrimal duct	Surgical excision, LRx (68 Gy)	Complete remission	None	22	None
Qiu *et al* 2013[6]	Sx (subtotal), Patient refused LRx	Local residue left behind	Spread of local residue	Sx (complete excision), LRx (60 Gy) to orbit	Complete remission	Neovascular glaucoma due to radiation, complete visual loss	33	None
Keelawat *et al* 2015[13]	Sx, Chemotherapy (Cb/5FU), LRx	33	None	N/A	N/A	None	33	N/A
Jakobiec *et al* 2015[14]	Sx (debulking), Patient awaiting LRx & chemotherapy	Patient awaiting treatment	N/A	N/A	N/A	N/A	No sufficient FU since tumour identification	N/A
Our case	Sx, LRx (66 Gy)	19	None	N/A	N/A	Radiation keratopathy, corneal ulceration, cataract, oral mucositis, periocular swelling, retinal neovascularisation, rubeotic glaucoma	30	N/A

DCT: Dacryocystectomy; DFS: Disease free survival; FNAB: Fine needle aspiration biopsy; LN: Lymph node; LRx: Local radiotherapy; RT: Radiotherapy; Sx: Surgical excision.

presentation. Majority of the patients (10, 91%) presented with symptoms and signs pointing towards the primary site of the malignancy. These cases did not show metastatic disease at presentation. The remaining patient (9%) presented with metastatic lymphadenopathy as the initial presentation. Retrospective examination of the CT scan of this patient who presented with ipsilateral metastatic submandibular lymphadenopathy, revealed an initially missed small solid ipsilateral lacrimal sac mass [8]. In all except in this case (91%) epiphora was a presenting feature. Six patients (55%) presented solely with epiphora and medial canthal swelling resembling a lacrimal sac mucocele. In nine patients the EBV association had been investigated. Seven out of these nine patients (78%) found to be positive for EBV RNA (EBER) in tumour cells. Two cases (22%) were negative for EBER. Other tests which indicated the relationship with EBV included EBV latent membrane protein-1 (ELMP-1) oncogene in tumour cells, serum IgA against EBV capsid antigen (EBV VCA IgA) and serum EBV early antigen and nuclear antigen-1 (EBV EA+NA1 IgA).

Treatment options and prognosis are summarised in the Table 2. Ten patients have received treatment prior to the publication of their cases. One patient was still awaiting treatment at the time of publication of the case [9]. 1) Surgery: ten out of 11 (91%) patients had been offered surgical excision or debunking. The extent of surgical excision depends on the extent of the tumour spread. In a small malignancy confined to the lacrimal sac may be removed by dacryocystectomy (DCT). Three of the patients (30%) were treated surgically treated with DCT. Other patients (70%) underwent more radical surgical excision procedures (Table 2). 2) Radiotherapy: in general UNPC has been reported to be sensitive to radiotherapy, with good locoregional tumor control at least in the short term [1]. All the patients in the above cohort had been offered adjuvant loco-regional radiotherapy. The dose of radiation ranged from 50-68 Gy. One patient, who initially refused radiotherapy in spite of only partial surgical removal of the tumour[6], responded well to subsequent treatment with 60 Gy radiation achieving complete remission. 3) Chemotherapy: four patients were offered chemotherapy as one option of the first line adjuvant treatment options [6-7,13-14]. One patient received chemotherapy as a second line treatment for disseminated disease. However, in this case the response to chemotherapy was poor and the patient died in spite of treatment [12]. Including our case, five cases (46%) responded to first line treatment with surgical excision/local radiotherapy/chemotherapy-achieving complete remission [7,10-11,13]. The disease-free interval of these patients ranged from 15 to 33mo. Three cases developed loco-regional relapses or metastases in spite of treatment[6,9,12]. Two of these cases responded to subsequent surgical excision, radiotherapy and/or chemotherapy with no recurrences or metastatic disease [6,9]. One patient developed mediastinal lymphadenopathy, pulmonary and skin metastasis and died 7mo after the initial surgery [12]. In one case the tumour was only partially excised by surgery and patient refused radiotherapy initially [6]. This patient responded to subsequent radiotherapy and achieved complete remission with no recurrences/metastasis during the subsequent 33mo follow up. One case presented with metastatic disease and the primary tumour was only discovered 12mo later [8]. The tumour metastasis and the primary site were both treated with surgery and radiotherapy and the patient responded very well to subsequent treatment with no reactivation of disease during the subsequent 24mo. Another case had been reported before receiving any treatment [14]. In this small cohort of ten patients (except the one patient had been published before receiving treatment) who received treatment, the overall short-term prognosis of the disease appears to be good with 90% achieving complete remission. Radiotherapy appears to be the most effective treatment modality.

The management of lacrimal drainage system malignancies is challenging due to their late presentation. They mimic symptoms and signs of idiopathic nasolacrimal outflow obstruction and in some instances these tumours are revealed during lacrimal surgical procedures. Primary UNPC of the ocular adnexa is very rare and the potential sites include the orbit[6], lacrimal gland[15], eyelid, and conjunctiva[6]. Before a diagnosis of a primary UNPC in the orbit or adnexa can be made, local invasion or metastatic spread from a primary undifferentiated nasopharyngeal carcinoma should be excluded [16-20]. The association between the (UNPC) and Epstein-Barr virus (EBV) is well established[2]. However, our patient was negative for EBV infection. Given the rarity of ocular adnexal UNPC, the optimal therapy is unclear [6]. Surgical excision alone cannot prevent recurrence and adjuvant radiotherapy with or without chemotherapy is crucial to prevent recurrence of UNPC. However, there is no long term follow up data available for this condition due to the rarity of the disease. High clinical suspicion for the presence of lacrimal sac mass in patients presented with epiphora is crucial for pertinent investigation and treatment. Although rare, lacrimal drainage system is a potential primary site for UNPC and it must be considered in the differential diagnosis of the lacrimal sac tumours.

The lacrimal drainage system malignancies mimic clinical features of idiopathic nasolacrimal outflow obstruction and this leads to delayed diagnosis in most cases. High clinical suspicion for the presence of lacrimal sac mass in patients presented with epiphora is crucial for pertinent investigation and treatment. Given the rarity of ocular adnexal UNPC, the optimal therapy is unclear and there is no long-term follow-up data. Surgical excision alone cannot prevent recurrences and adjuvant radiotherapy with or without chemotherapy is crucial to prevent recurrence of UNPC. Because of its tendency to metastasize these patients may benefit from lifelong follow-up.

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