Case Report

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Primary ductal adenocarcinoma of lacrimal gland: Two case reports and review of the literature

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Abstract:

A 64-year-old male presented with progressive proptosis of the left eye for 3 months. Orbital computed tomography (CT) demonstrated a 3.9 cm infiltrative mass over the superotemporal quadrant of the left orbit. Pathology of biopsy revealed a ductal adenocarcinoma of lacrimal gland with positive immunohistochemical staining for androgen receptor (AR), cytokeratin-7 (CK7), and gross cystic disease fluid protein 15 (GCDFP-15). The patient received orbital exenteration and adjuvant chemoradiotherapy. No recurrence or metastasis was noted 27 months after treatment. Another case was a 64-year-old male who came for proptosis of the right eye and diplopia for 3 weeks. Orbital CT revealed a 5 cm infiltrated right superotemporal orbital mass with destruction of the lateral and inferior orbital walls. Biopsy showed primary ductal adenocarcinoma of lacrimal gland with positive immunohistochemical staining for CK7, AR, and epidermal growth factor receptor. The patient underwent exenteration and concomitant chemoradiotherapy. However, lung and neck metastasis was noted 21 months after surgery. Collectively, 26 cases in the literature were reviewed. The mean age was 57 years old and male was prevalent (73%). Most immunohistological staining showed positive for AR (46%), CK7 (46%), Ki-67 (38%), and GCDFP-15 (35%). More than half of the patients developed metastasis and one-third of the patients died of disease. Early diagnosis, treatment, and long-term follow-up are required for this aggressive tumor.

Keywords:

Androgen receptor, exenteration, immunohistochemical staining, lacrimal gland, primary ductal adenocarcinoma

Introduction

Primary ductal adenocarcinoma of lacrimal gland is a distinct subtype of lacrimal gland adenocarcinoma, accounting for only 2% of all epithelial lacrimal gland tumors.[1] There are only some sporadic cases reported in the literature. Primary ductal adenocarcinoma of lacrimal gland is generally thought to be an aggressive malignancy; however, their clinical features, treatment, and outcome remained not well understood. In this study, we report two cases of adenocarcinoma of the lacrimal gland with a review of the literature.

Case Reports

Case 1

A 64-year-old male presented with progressive proptosis of the left eye for 3 months [Figure 1a]. He denied any systemic disease or surgical history before. On examination, the best-corrected visual acuity was 6/6 in both eyes. There was 5 mm of proptosis in the left eye compared with the right eye. Eye movement was limited in the upper gaze of the left eye. Other ophthalmic examination results were unremarkable. Orbital computed tomography (CT) revealed a 3.9 cm × 2.2 cm × 3.7 cm lobulated mass with lateral orbital wall

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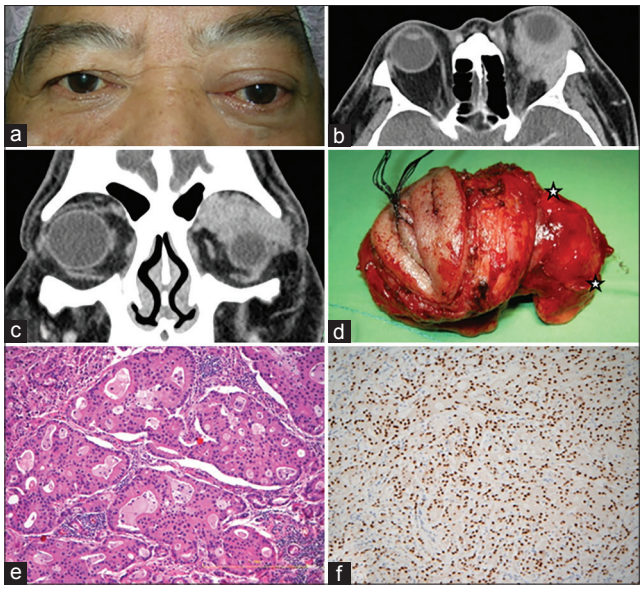

Figure 1: (a) Case 1 presented with proptosis and inferior displacement of the left globe. (b and c) Axial and coronal orbital computed tomography demonstrates a tumor about 3.9 cm × 2.2 cm × 3.7 cm in size in the superotemporal orbit. (d) Gross pathology of the excised specimen and tumor marked with stars. (e) Microscopic findings reveal ductal structures with abundant granular eosinophilic cytoplasm (H and E, ×100). (f) Immunostain shows strong expression of androgen receptor (×100)

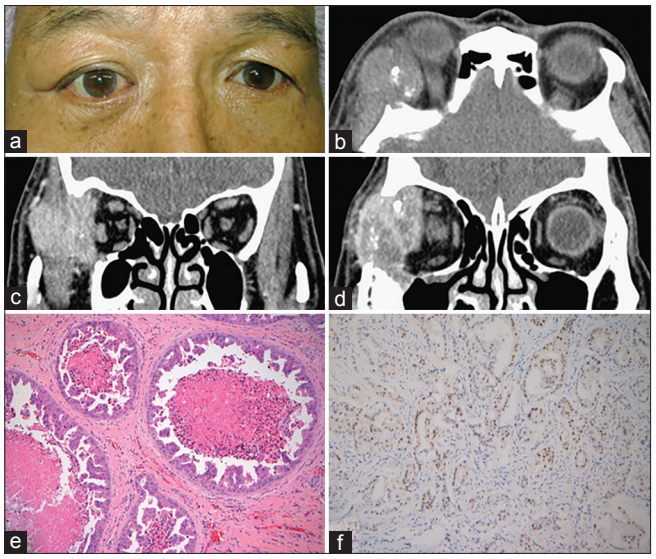

Figure 2: (a) Case 2 manifested as proptosis and inferior displacement of the right globe. (b-d) Axial and coronal orbital computed tomography demonstrates an infiltrated tumor mass in the lateral orbit of the right eye and destruction of lateral and inferior orbital wall with extension to deep temporal fossa. Focal calcification in the tumor is noted. (e) Microscopic findings revealed ductal structure with comedo necrosis (H and E, ×100). (f) Immunostain shows positive nuclear expression for androgen receptor (×100)

erosion [Figure 1b and c]. Laboratory survey showed no significant findings. He underwent incisional biopsy, and histopathological examination revealed an infiltrative tumor composed of tumor cells with eosinophilic cytoplasm and prominent nucleoli arranged in an irregular glandular pattern. The tumor cells were immunoreactive for androgen receptor (AR) and cytokeratin-7 (CK7). Immunostains for cytokeratin-20 (CK20), thyroid transcription factor-1 (TTF-1), and prostatic-specific antigen were negative. The above findings are compatible with primary ductal adenocarcinoma of lacrimal gland. Whole-body positron emission tomography (PET)-CT showed no evidence of systemic involvement. He then underwent an orbital exenteration which the gross examination revealed a white firm tumor measuring 3.5 cm × 8 cm × 5 cm [Figure 1d]. The tumor was composed of nests of cuboidal and columnar cells with eosinophilic cytoplasm and vesicular nuclei and occasional mitosis. The tumor cells were arranged in ductal structures of varying sizes, allying with cribriform pattern [Figure 1e]. Mucin secretion was seen in some ductal lumens. Lymphovascular emboli and perineural invasion were also found. Immunohistochemical stains for CK7 [Figure 1f], AR, and gross cystic disease fluid protein 15 (GCDFP-15) were positive. The final diagnosis was primary ductal adenocarcinoma of lacrimal gland, staging T4N0M0. The patient subsequently received adjuvant chemoradiotherapy. He took the radiation dose of 6800cGy in 34 fractions at superior and lateral surgical bed, 6120cGy in 34 fractions at the other surgical bed, and 5780cGy in 34 fractions at the left parotid gland and neck lymph node. At the same time, he received cisplatin and tegafur-uracil weekly for seven cycles as chemotherapy. There was no evidence of recurrence or metastasis 27 months after treatment.

Case 2

A 64-year-old male presented with proptosis of the right eye and diplopia for 3 weeks [Figure 2a]. On ophthalmic examination, best-corrected visual acuity was 6/20 in the right eye and 6/8.6 in the left eye. Ocular movement showed limited abduction of the right eye. Hertel exophthalmometry showed 5 mm of proptosis of the right eye compared with the left eye. Other ophthalmic examination results were unremarkable. Orbital CT showed a mass lesion about 5 cm × 5 cm × 3.3 cm in the right lateral orbital with extensive bony destruction and extension to deep temporal fossa [Figure 2b-d]. The patient underwent orbital biopsy which revealed primary ductal adenocarcinoma of lacrimal gland. Immunohistochemical stain showed positive for CK7, AR, and epidermal growth factor receptor (EGFR) but negative for CK20 and TTF-1. Whole-body PET-CT showed no evidence of systemic involvement. Then, he underwent radical surgery with orbital exenteration and removal of adjacent lateral and inferior orbital wall and reconstruction with metal plate and free myocutaneous flap. Histological studies showed an infiltrative tumor composed of pleomorphic tumor glands, which resemble high-grade ductal carcinoma *in situ* and infiltrating carcinoma of the breast. The tumor cells have eosinophilic cytoplasm, enlarged nuclei, and prominent nucleoli [Figure 2e]. There is also a hyalinized nodule in the center of the

tumor. Bony, perineural, and lymphovascular invasion was noted. Immunohistochemically, the tumor is positive for AR [Figure 2f]. The patient then underwent concomitant chemoradiotherapy. He received six cycles of cisplatin and tegafur-uracil weekly and radiotherapy with 6600cGy in 33 fractions at surgical bed and 5040cGy in 28 fractions at the right orbital flap. However, distant metastasis to neck lymph nodes and bilateral upper lobes of the lung was noted at the 21st month of follow-up. Total parotidectomy of the right parotid gland and modified radical neck dissection were performed. The patient refused further chemoradiotherapy and lost to follow-up.

Discussion

Primary ductal adenocarcinoma of lacrimal gland was first reported by Katz *et al*. in 1996.[2] The pathological characteristics are similar to salivary duct carcinomas and ductal carcinomas of the breast. The clinical features and treatment outcome were not well constructed because sparse cases were reported.

We retrospectively review 24 collected and our 2 new cases of primary ductal adenocarcinomas of lacrimal gland in the literature [Table 1].[3-20] The mean age of the 26 patients was 57 years old and most cases were males (73%). Two of them had pleomorphic adenoma at the same location[4,13] and one had a history of neurofibromatosis.[18] The most common presenting symptom was exophthalmos. The typical appearance of this tumor in orbital CT showed irregular shape lesion with focal destructive change at lacrimal gland area. Adjacent extraocular muscle or bony invasion was not rare. Some cases also showed calcifications in CT image as in our case two.[5,11,17] Early diagnosis is crucial because the tumor was pretty aggressive because these patients had a mean tumor size of 3 cm in diameter (ranges from 1.1 to 5 cm) at initial examination, and metastasis was seen during follow-up in 15 patients (58%). The diagnosis was confirmed by pathological analysis, and the typical appearance of the tumor is ductal structure with abundant granular eosinophilic cytoplasm. Comedo necrosis in the duct may present. Immunohistological examinations of primary ductal adenocarcinoma of lacrimal gland often showed positive to AR (46%), CK7 (46%), Ki-67 (38%), GCDFP-15 (35%), human EGFR-2 (Her-2) (35%), and p53 (35%), which are similar to salivary duct carcinomas and ductal carcinomas of the breast. It is reported that salivary duct carcinomas showed 93% positive result of AR while 1% and 6% in estrogen receptor (ER) and progesterone receptor (PR), respectively.[21] Breast cancer showed more than 50% positive rate of ER and PR.[22] According to the immunohistological finding of ductal adenocarcinomas of lacrimal gland, positive expression of AR while negative of ER and PR may indicate that the biological character of the tumor was more similar to salivary duct carcinomas. Clinically, aggressive presentation of salivary duct carcinomas is similar to primary ductal carcinomas of lacrimal gland as it was documented 46% of patients developed distant metastasis[23] among the former while 15 patients (58%) showed the evidence of metastasis in our collected cases [Table 2]. Therefore, the treatment for primary ductal adenocarcinomas of lacrimal gland may refer to the treatment for salivary duct carcinomas as there are more documents of efficacy in the latter. Salivary duct carcinomas are mostly treated by surgery and possible radiochemical therapy according to staging. In addition, there were some reports that androgen deprivation therapy could be beneficial for patients with recurrent or disseminated disease.[24] In our collected cases, Ricci *et al*.[5] reported a case of primary ductal adenocarcinoma of lacrimal gland with L1 spine metastasis treated by total androgen blockage therapy, where the patient survived more than 10 months. Moreover, there are also some reports showing that with positive Her-2, a proto-oncogene which is overexpressed in salivary duct carcinomas and breast ductal carcinomas, the patients treated with monoclonal antibody against EGFR such as trastuzumab may improve prognosis in both salivary duct carcinomas[25] and breast ductal carcinomas.[26] Dennie[7] reported a case of primary ductal adenocarcinoma of lacrimal gland who was treated with lapatinib, an oral tyrosine kinase inhibitor against Her-2 and EGFR, survived 4 years after diagnosis. The efficacy of chemotherapy was uncertain as there are only two prior documented cases receiving adjuvant chemoradiotherapy in the literature besides our two cases. Giliberti *et al*.[10] reported the patient received carboplatin, paclitaxel, and herceptin as chemotherapy after surgery. However, the clinical course after chemotherapy was not recorded. Kim *et al*.[15] reported a case who died of disease 17 years after treatment with surgery and chemoradiotherapy, but regiment detail was not documented. Due to their rarity, the effectiveness of chemotherapy in primary ductal adenocarcinoma of lacrimal gland requires further investigation. Among the 26 collected cases, more than half of the patients received exenteration and/or adjunct radiotherapy and/or chemotherapy (58%). Even after aggressive treatment, nine patients (35%) died of disease, including one patient who died of disease 17 years after diagnosis. The cause of death was mostly distant metastasis including cervical lymph node (31%), brain (23%), bone (23%), lung (23%), and liver (15%). The reason why our two cases resulted in different prognosis may be that the tumor in the second case showed more extensive infiltration and bony destruction at initial diagnosis. Furthermore, the first case received additional prophylactic neck lymph node radiation after orbital exenteration, which was not performed in the second case. Prophylactic lymph node irradiation might benefit for locally advanced head-and-neck tumors.[27]

Table 1: Clinical features and immunohistological staining characteristics for 26 reported cases of primary ductal adenocarcinoma

Literature	Age	Sex	Symptoms	Site	Maximum diameter (cm)	Immunostain (+)	Immunostain (–)
Our case 1	64	Male	Orbital mass and proptosis for 3 months	Left	3.9	AR, CK7, GCDFP-15	CK20, TTF-1, PSA, S-100
Our case 2	64	Male	Proptosis and diplopia for 3 weeks	Right	5	AR, CK7, EGFR	CK20, TTF-1
Andreasen *et al*. 2017[9]	77	Male	Diplopia for 2 weeks	Left	3.2	AR, CK7, CK17, CK19, Cyclin D1, EGFR, EMA, GCDFP-15, Her-2, p53, Ki-67	CEA, CK5/6, DOG1, ER, PR, PSA, S-100, □-SMA
	53	Male	Proptosis of the left eye for 5 years	Left	2	CK5, CK6, CK7, CK19, Cyclin D1, EGFR, EMA, Her-2, p53, AR, CEA, CK17, GCDFP-15, Ki-67	DOG1, ER, PR, PSA, S-100, □-SMA
	73	Male	Proptosis for 5 years	Right	4	CK7, CK19, EGFR, EMA, Her-2, p53, CEA, CK17, Cyclin D1, GCDFP-15, Ki-67	AR, CK5/6, DOG1, ER, PR, PSA, S-100, □-SMA
Dennie, 2015[7]	53	Female	Headache, blurred vision, and proptosis	Right	3	Keratin, CK7, mammaglobin	CK20, TTF-1, GCDFP-15, ER, PR
Lau *et al*. 2015[8]	34	Female	Right upper eyelid swelling for 1 year	Right	2.8	EMA, CD117, PAS	S-100, CK20, Melan A
Zhu *et al*. 2015[3]	49	Female	Painless, palpable mass, double vision, and epiphora for 6 months	Left	1.1	GCDFP-15, AR, Her-2, p53, Ki-67, CK18	ER, PR, P63, calponin, CD117
Ricci *et al*. 2014[5]	71	Male	Lumbar pain for 3 years and slight exophthalmos for several years	Right	2.3	AR, GCDFP-15, CK7, Her-2	TTF-1, PSA, ER, PR, CK20, CDX2
Min *et al*. 2014[6]	46	Male	Exophthalmos and blurred vision for 2 months	Left	3	CK5, CK7, CK20	S-100, TTF-1, PSA
Kubota *et al*. 2013[11]	75	Male	Upper eyelid swelling for 3 months	Right	2.8	AR, Her-2, p53, Ki-67	ER, PR
	67	Male	Upper eyelid swelling and ptosis for 6 months	Left	4	AR, p53, Ki-67	Her-2, ER, PR
	53	Male	Upper eyelid swelling and ptosis for 18 months	Right	3.7	AR, p53, Ki-67	Her-2, ER, PR
	39	Male	Upper eyelid swelling for 6 months	Left	2.5	AR, Her-2, p53, Ki-67	ER, PR
	46	Female	Upper eyelid swelling for 1 months	Right	2.5	AR, Her-2, p53, Ki-67	ER, PR
Damasceno and Holbach, 2012[12]	78	Male	Diplopia, painless, palpable mass, and restricted abduction	Right	2.4	CK7, MMP2, MMP9, MMP13, Her-2	CK5, CK20, p63, PSA, S-100, TTF-1
Giliberti *et al*. 2011[10]	17	Male	Right orbital mass for 6 months	Right	NA	NA	NA
Ishida *et al*. 2009[13]	70	Female	Painful exophthalmos	Left	2.5	GCDFP-15, Ki-67	AR, Her-2, ER, PR
Lee and Oh, 2009[14]	50	Male	Exophthalmos	Right	4	CK7, CK19, EMA	Her-2, ER, PR, CK20, p53, S-100, □-SMA
Kim *et al*. 2008[15]	47	Male	Left lacrimal gland mass	Left	NA	NA	NA
Takahira *et al*. 2007[4]	48	Female	Progressive exophthalmos for 3 years	Left	3.8	AR, GCDFP-15	ER, PR
Milman *et al*. 2005[16]	59	Male	Orbital mass and blepharoptosis 15 years	Right	1.5	GCDFP-15, keratin AE1, CK7, CEA, EMA, CK20	TTF-1, PSA, Her-2, ER, p53, S100
Kurisu *et al*. 2005[17]	67	Male	Visual disturbance	Right	3	CK7, CK10, CK17, CK18, CK19	S-100, □-SMA, CK20
Krishnakumar *et al*. 2003[18]	46	Male	Firm irregular mass with progressive ptosis in the orbit 2 years	Left	NA	NA	NA

Contd...

Table 1: Contd...

Literature	Age	Sex	Symptoms	Site	Maximum diameter (cm)	Immunostain (+)	Immunostain (–)
Paulino and Huvos, 1999[19]	52	Female	NA	Right	NA	NA	NA
Nasu *et al*. 1998[20]	67	Male	Small nodule in the upper eyelid	Right	2.5	EMA, CK, CEA, S-100	Actin, ER, PSA
Katz *et al*. 1996[2]	68	Male	Lump in the upper outer eyelid	Right	4	Keratin	HMB-45, NSE, S-100, chromogranin, CEA, PSA

AR=Androgen receptor, CDX2=Caudal-type homeobox 2, CEA=Carcinoembryonic antigen, CK=Cytokeratin, EGFR=Epidermal growth factor receptor, EMA=Epithelial membrane antigen, ER=Estrogen receptor, GCDFP-15=Gross cystic disease fluid protein 15, Her-2=Human epidermal growth factor receptor 2, MMPs=Matrix metalloproteinases, NA=Not available, NSE=Neuron-specific enolase, PAS=Periodic acid–Schiff, PR=Progesterone receptor, PSA=Prostate-specific antigen, SMA=Smooth muscle actin, TTF-1=Thyroid transcription factor-1

Table 2: Initial staging, treatment, and outcome for 26 reported cases of primary ductal adenocarcinoma

Literature	Initial staging	Treatment	Metastasis	Outcome
Our case 1	T4N0M0	Exenteration, RT and CT	Nil	AOD at 2.25 years
Our case 2	T4N0M0	Exenteration with bone removal, RT, and CT	Right neck LN, lung	AWD at 1.75 years
Andreasen *et al*. 2017[9]	T4bN0M0	Exenteration and RT	Nil	DO at 1.6 years
	T1N0M1	Nil	Lung, liver, suprarenal glands, vertebral column, cerebellum; LN of the neck, thorax, abdomen, and thorax	DWD at 5 years
	T4bN0M0	Tumor excision and RT	Disseminated disease	DWD at 1.4 years
Dennie, 2015[7]	T4cN0M0	Exenteration, RT, and target therapy	Chest and thorax spine, cerebellum, lung	DWD at 4 years
Lau *et al*. 2015[8]	T2N0M0	Tumor excision	Nil	AOD at 0.17 years
Zhu *et al*. 2015[3]	T1N0M0	Exenteration and RT	Nil	AOD at 0.75 years
Ricci *et al*. 2014[5]	T2NxM1	Exenteration, RT, and total androgen blockade	L1 spine	AWD at 1.6 years
Min *et al*. 2014[6]	T4bN0M0	Orbital mass removal and RT	Nil	AOD at 0.4 years
Kubota *et al*. 2013[11]	T4bN1M0	RT to ocular adnexa and surgical resection of submandibular LN	Cervical LN, lung	DWD at 2 years
	T2N0M0	Exenteration with bone removal	Submandibular LN, bone, and liver	DWD at 1.3 years
	T4aN0M0	Exenteration and RT	Spine, brain, liver	DWD at 4.3 years
	T4bN0M0	Exenteration with bone removal and RT	Lung, brain	AWD at 10 years
	T2N0M0	Complete tumor resection with globe-sparing surgery	Nil	AOD at 5.5 years
Damasceno and Holbach, 2012[12]	T2N0M0	Exenteration	Ipsilateral parotid and cervical LN	DWD at 2 years
Giliberti *et al*. 2011[10]	T4cN0M0	Exenteration	Nil	AOD at 0.5 years
Ishida *et al*. 2009[13]	T2NxMx	Tumor resection twice for recurrence and RT	NA	AWD at 0.7 years
Lee and Oh, 2009[14]	T2N0M0	Tumor resection (en bloc) with globe-sparing surgery	NA	AOD at 0.8 years
Kim *et al*. 2008[15]	NA	Exenteration, RT, and CT	Chest skin, lymphatics, ilium, rib, femur, spine, orbit, postnasal region, L-spine, cerebellum	DWD at 17 years
Takahira *et al*. 2007[4]	T2N0M0	Total tumor excision and RT	Nil	NA
Milman *et al*. 2005[16]	T1N1M1	Exenteration and RT	Parotid, cervical LN	AWD at 0.5 years
Kurisu *et al*. 2005[17]	T2N0M0	En bloc tumor resection and RT	Local recurrence; brain, lungs, liver, pancreas, common bile duct	DWD at 2.8 years
Krishnakumar *et al*. 2003[18]	NA	Exenteration and RT	Nil	AOD at 1.6 years
Paulino and Huvos, 1999[19]	TxN1Mx	Exenteration and RT	Neck LN	AOD at 6 years

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Table 2: Contd...

Literature	Initial staging	Treatment	Metastasis	Outcome
Nasu *et al*. 1998[20]	T2NxMx	En bloc tumor resection with frontal craniotomy and RT	Sella turcica to the subdural spaces of the right temporal lobe	AOD at 2 years
Katz *et al*. 1996[2]	T4aN0M0	Frontotemporal craniotomy, en bloc orbitectomy, and RT	Nil	AOD at 0.8 years

AOD=Alive without disease, AWD=Alive with disease, CT=Chemotherapy, DO=Died of other cause, DWD=Died with disease, LN=Lymph node, NA=Not available, Nil=No evidence of metastasis, RT=Radiotherapy

Conclusions

Primary ductal adenocarcinoma of lacrimal gland is a high-grade epithelial tumor similar to salivary ductal carcinomas. Early and timely diagnosis and management and long-term follow-up are required for this aggressive tumor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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