• Brief Report •

Lacrimal gland pleomorphic adenoma: two referral center analyses in Hokkaido, Japan

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Abstract

• **AIM:** To evaluate the clinical features of primary lacrimal gland pleomorphic adenoma (LGPA).

• **METHODS:** This was a 2-center, retrospective, observational study of primary LGPA patients who underwent tumor resection. Ophthalmic examinations and orbital computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed.

• **RESULTS:** Totally 18 patients (10 males and 8 females, mean age 56.3±13.8y) were enrolled. Initial symptoms were unilateral proptosis in 8 patients, diplopia in 3 patients, and pressure sensation and no chief complaint in 2 patients each. The best-corrected visual acuity of the affected eye was 0.26±0.44 logMAR, and the intraocular pressure (IOP) of the affected and healthy eyes was 20.1±9.9 and 15.8±4.3 mm Hg, respectively. The difference in degree of proptosis between the affected and healthy eyes was 4.1±2.2 mm based on the Hertel ocular protrusion meter. One case had a history of breast cancer. Seventeen of 18 patients with an orbital lacrimal gland origin underwent total tumor excision by anterior/lateral orbitotomy.

• **CONCLUSION:** Orbital LGPA can complicate IOP elevation, and require total tumor excision by orbitotomy. In rare cases, systemic malignancy may complicate LGPA, and in such cases total removal of the lacrimal gland tumor should be considered at the initial surgery.

• **KEYWORDS:** lacrimal gland pleomorphic adenoma; anterior/lateral orbitotomy; proptosis; breast cancer
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INTRODUCTION

Lacrimal gland pleomorphic adenoma (LGPA) accounts for 12%–25% of lacrimal gland tumors and is the most common benign primary epithelial tumor of the orbit[1-2]. LGPA shows a diverse histopathologic picture, comprising epithelial and stromal-like tissue components. However, epithelial tumors have a propensity to recur if incompletely excised[3]. When imaging and clinical findings are suggestive of LGPA, diagnostic biopsy is not recommended because of the possibility of tumor recurrence[3]. In fact, recurrence rates following biopsy or incomplete resection of the tumors are likely to increase over a 5-year period[4]. In recent years, as a result of improved radiological imaging evaluation, the rate of inadvertent biopsies of LGPA has decreased[4]. Thus, clinical diagnosis based on imaging modalities is crucial to avoid unnecessary biopsy.

Surgical intervention by means of anterior/lateral orbitotomy is an important technique for complete resection of orbital tumors with an intact capsule[3], whereas incomplete excision of the capsule or its loss at surgery can lead to significantly higher recurrence rates caused by seeding of tumor cells into the orbit[5-6]. When lesions are completely excised with an intact capsule, the prognosis is good, with a recurrence rate of less than 3% at 5y[3]. It is more difficult to treat recurrent than primary tumors because the former often comprise multiple lesions[7] and further invade normal orbital structures[3]; in some cases, orbital exenteration or radiation therapy may be considered for rare inoperable massive pleomorphic

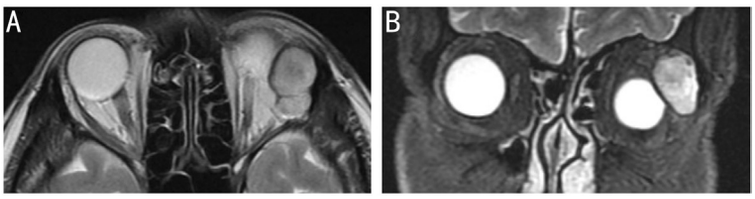

Figure 1 Imaging in a case with high intraocular pressure A: T2-weighted magnetic resonance imaging (MRI) of a coronal section showed a heterogeneous mass in the orbit of the left lacrimal gland region measuring 21.2×18.3×24.1 mm^3; B: T2-weighted MRI of an axial section showed medial inferior deviation of the left eyeball.

adenomas or recurrent/remnant lesions. Moreover, malignant transformation to carcinoma has been reported in a Japanese population[8], emphasizing the importance of removing the entire tumor at the initial surgery. However, to totally remove orbital LGPA, special techniques including anterior/temporal excision of orbital bones are usually needed. Therefore, since a limited number of centers can treat LGPA in Japan, the details of its clinical characteristics in the real-world remain largely unknown.

The aim of this study was to evaluate the clinical features, imaging findings, and surgical outcomes, and propose management of a primary LGPA patient with a history of systemic cancer.

PARTICPANTS AND METHODS

Ethical Approval This retrospective, observational study was approved by the Institutional Review Board of Hokkaido University Hospital (IRB number: 023-0052) and Teine Keijinkai Hospital (IRB number: 1-023442-00). This study complied with the Declaration of Helsinki.

At the former hospital, 12 patients, including 2 patients as representative cases, gave informed consent for the use of their imaging and clinical and pathological information in publications. The IRB at Teine Keijinkai Hospital approved the study on an opt-out basis, in which patients were given the opportunity to refuse to participate in the study *via* the website, since this was a non-invasive retrospective observational study. Patients histologically diagnosed with LGPA between January 2010 and May 2023 were enrolled.

Ophthalmic examinations including best-corrected visual acuity, intraocular pressure (IOP), slit-lamp microscopy, ocular position, eye movement, external ophthalmoscopy, Hertel ocular protrusion meter, and fundus examination were performed in all patients. Then, orbital computed tomography (CT) and/or magnetic resonance imaging (MRI) were examined. The tumors were diagnosed as primary LGPA based on histopathological examinations at each institution. Patients with other types of ocular adnexal epithelial tumors, such as adenoid cystic carcinoma, adenocarcinoma, carcinoma ex pleomorphic adenoma, and metastatic tumor, were excluded. The surgical technique for orbital LGPA was reported by Watanabe *et al*[9].

RESULTS

Clinical Features This study eventually enrolled 18 consecutive LGPA patients with 18 tumors. The patients were 10 men and 8 women; the meian age at the time of initial presentation was 56.3±13.8y (range: 27-85y). Initial symptoms were proptosis in 8 patients, diplopia in 3 patients, pressure sensation and no chief complaint in 2 patients each, and eyelid swelling, ptosis and decreased visual acuity in 1 patient each. The logMAR best-corrected visual acuity of the affected eye was 0.26±0.44, and IOP of the affected and healthy eyes was 20.1±9.9 and 15.8±4.3 mm Hg, respectively. In 3 cases, IOP of the affected eyes differed by more than 9 mm Hg compared with the healthy eyes. The difference in the degree of proptosis between the affected and healthy eyes was 4.1±2.2 mm based on the Hertel ocular protrusion meter.

Orbital CT detected an iso-intense mass in the lacrimal region and thinning of the frontal bone (remodeling), but no case showed bone invasion. Calcification was seen in one case. MRI detected a mass with heterogeneous signal intensity on T2-weighted images (WI). One case was already reported as gourd-shaped LGPA[10]. Three cases, in which IOP in the affected eye was high (Figure 1), had respective tumor volumes of 15.7, 9.1, and 20.1 cm^2 on MRI or CT.

In all cases, total orbital tumor resection was performed at the first surgery based on the clinical diagnosis without an incisional biopsy. Seventeen of 18 patients with orbital lacrimal gland origins and a location posterior to the ocular equator underwent total tumor resection by anterior/lateral orbitotomy. Simple tumor resection through a transcutaneous approach was conducted in one case with LGPA extending to the upper and lower orbit. In 5 of the 9 patients for whom detailed surgical records were available, the tumor was completely removed intact without obvious capsular damage. The postoperative IOP of 2 cases, in which IOP in the affected eyes was high, dropped to the same level as those in the healthy eyes. One case, with persistently elevated IOP, received topical glaucoma agents and subsequent additional cataract surgery and anterior vitrectomy. One patient (the first representative case) showed suspicious recurrence 3y after surgery and another patient (the second representative case) had a history of breast cancer.

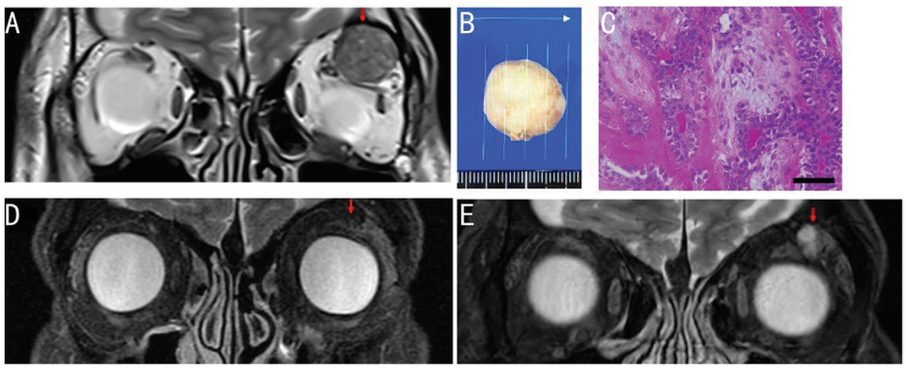

Figure 2 Imaging and pathological findings in the first representative case A: T2-weighted magnetic resonance imaging (MRI) showed a heterogeneous well-circumscribed mass. B: The pathology specimen showed that the tumor was resected as one lump. C: Histopathological findings showed bilayer proliferation of short spindle-shaped myoepithelial cells and epithelial cells forming tubular or cord-like structures against a background of some mucous-like and cartilage-like matrix (hematoxylin-eosin stain, 40× magnification). Bar indicates 40 μm. D: T2-weighted fat suppression orbital MRI 1y after surgery showed no apparent recurrence. E: T2-weighted fat suppression orbital MRI 8y after surgery revealed a nodular mass on the dorsal surface of the left lacrimal gland that had enlarged to approximately 10 mm.

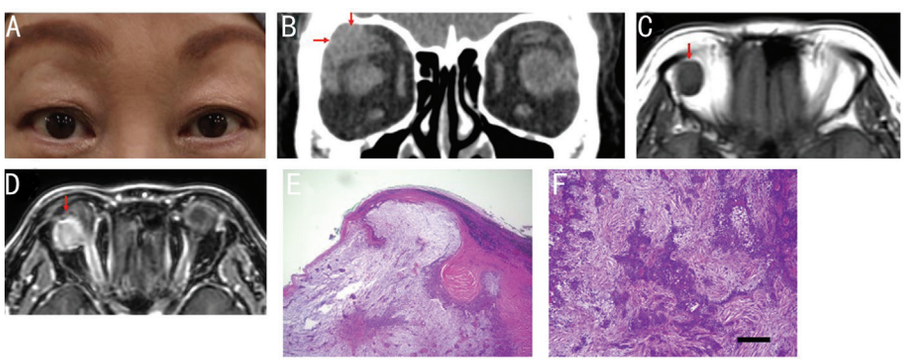

Figure 3 Imaging and pathological findings in the second representative case A: No obvious mass lesions were palpable at the initial examination; B: Coronal image of computed tomography at the initial visit showed a uniform mass with well-defined borders and an irregular shape in the right superior orbit; C: T1-weighted orbital magnetic resonance imaging (MRI) showed a low-signal mass; D: Contrast-enhanced orbital MRI showed a 15-mm mass in the right supraorbital region with contrast enhancement; E: Histopathological findings revealed a mass with thin fibrous capsule (hematoxylin-eosin stain, 4× magnification); F: Histopathological findings showed a bilayer of myoepithelial-like cells with poor atypia and epithelial-like cells inside, forming an adenoductal structure with little atypia (hematoxylin-eosin stain, 10× magnification).

The First Representative Case A 44-year-old male who complained of pressure sensation in his left eye was referred to our department because of proptosis and limitation of upper movement of the left eye. There was no relevant medical history. T2-weighted orbital MRI showed a heterogeneous well-circumscribed mass identified within the lacrimal fossa (Figure 2A, red arrow). Total excision of the tumor was performed by anterior/lateral orbitotomy. The mass was entirely resected in one lump without damaging the capsule (Figure 2B). Histopathological findings showed bilayer proliferation of short spindle-shaped myoepithelial cells and epithelial cells forming tubular or cord-like structures against a background of some mucous-like and cartilage-like matrix (Figure 2C). The capsule was mostly intact, with some intracapsular invasion, but there were no malignant findings, and no exposed margins. T2-weighted fat suppression orbital MRI 1y after the surgery showed no apparent recurrence (Figure 2D). However, an about 10-mm nodular mass on the dorsal surface was noted in the left orbit on T2-weighted fat suppression MRI 3y after the surgery, and the patient continued to be observed every 6mo due to potential recurrence. Eight years later, MRI showed the tumor had enlarged (Figure 2E) and re-excision was scheduled.

The Second Representative Case A 63-year-old female was diagnosed with invasive ductal carcinoma of the bilateral breasts, and was referred to our ophthalmology department because MRI for systemic examination incidentally detected a right orbital tumor. She had a medical history of urticaria. No obvious mass lesions were palpable in the eyelid (Figure 3A). Orbital CT showed a mass in the right supraorbital region (Figure 3B, red arrows). There was neither obvious bone invasion nor calcification. T1-weighted orbital MRI showed a low-signal demarcated mass (Figure 3C, red arrow) and contrast-enhanced MRI showed a 15-mm mass in the right

supraorbital region with contrast enhancement (Figure 3D, red arrow). Total excision of the tumor was performed by anterior/lateral orbitotomy. Histopathological findings revealed a mass with thin fibrous capsule and a bilayer of myoepithelial-like and epithelial-like cells inside with poor cellular atypia, forming adenoductal structures (Figure 3E and 3F). No malignant findings including metastatic invasive ductal carcinoma were noted. The patient has been followed up for 2y since surgery without local recurrence.

DISCUSSION

In this study, we analyzed the clinicopathological findings in 18 LGPA patients at two institutions in Hokkaido, Japan. LGPA is usually a painless, slow-growing mass with proptosis and diplopia[3]. In a previously reported case series of 109 patients with LGPA, the male to female ratio was 1:1.6, mean age was 43.6y, and 5-year recurrence rate was 7.3%[6]. In a previously reported case series of 37 patients with LGPA in Japan[9], the male to female ratio was 1:1.5, and the mean age was 51.9y. Imaging findings including orbital CT showed well-defined isointense lesions (94.2%)[11], often with calcification (12%)[9]. Orbital MRI typically shows a low-to-isointense signal on T1-WI[9,11], heterogeneity on T2-WI, and limbal enhancement (27%) on T1-WI fat-suppressed gadolinium-enhanced MRI[9]. Bone excavation was observed in 84% of orbital-lobe LGPA with an enhancing rim visible on T1-WI fat-suppressed gadolinium-enhanced MRI[9]. In this study, the male-to-female ratio (10:8) was high, and the age of the patients (56.3±13.8y) was advanced compared with previous reports. There was one patient (6%) with calcification among the 17 patients with CT imaging, being fewer than that in previous reports. Although elevated IOP is rare in benign tumors of the lacrimal gland area[12], interestingly, postoperative IOP in our 2 cases, in which the affected eye showed high preoperative IOP, dropped to the same level as that in the normal eye, suggesting an effect of ocular compression due to an increased periorbital tissue volume (Figure 1), which would be similar to thyroid eye disease. In one case, preoperative long-term elevation of IOP due to chronic angle closure by tumor compression could not be resolved even after tumor resection. Therefore, urgent total tumor resection is recommended when IOP elevation is observed in patients with LGPA.

Incisional biopsy, incomplete resection, and damage to the capsule surrounding the tumor may increase the risk of recurrence and malignant transformation due to tumor cell dissemination[2]. Although there are rare cases of LGPA extending to the inferior orbit (Case 4)[10] and of LGPA arising from ectopic lacrimal gland tissue[13], total resection should basically be attempted without biopsy in cases when LGPA is suspected. Conversely, Jakobiec *et al*[14] reported a patient with breast cancer showing rare pathological findings of LGPA; however, there are no reports describing clinical findings and management of LGPA arising in patients with systemic cancer including breast cancer that could metastasize to the lacrimal gland. Therefore, lacrimal gland tumors in patients with systemic cancers require careful consideration regarding whether to perform biopsy or total tumor resection by anterior/lateral orbitotomy based on the preoperative clinical diagnosis. In this study, total orbital tumor resection was performed at the first surgery based on clinical diagnosis without incisional biopsy in all patients with primary LGPA.

Lacrimal gland metastases from breast cancer are very rare. In a report of two women with a history of invasive ductal carcinoma of the breast, a rapidly growing lacrimal gland tumor was noted[15]. CT showed a mass involving not only the lacrimal gland, but also the external and superior rectus muscles with bone invasion, and biopsy specimens proved breast cancer metastasis[15]. Another case report showed lacrimal gland metastasis from invasive lobular carcinoma as the first manifestation of disseminated breast cancer[16]. In our patient with breast cancer, the imaging findings and tumor growth rate were different from those previously reported for lacrimal gland metastasis of breast cancer. If imaging findings and tumor growth had been more suspicious for lacrimal gland metastasis of systemic cancer, prompt incisional biopsy should have been initially considered.

In this study, one patient (the first representative case) showed suspicious recurrence 3y after surgery. Few reports have shown orbital MRI of recurrent cases of LGPA, but it has been reported that T2-WI showed pearly nodular lesions with high signals and 4–5 mm in diameter[7]. As factors influencing the recurrence of LGPA, the disease course, tumor diameter, bone destruction, invasion of surrounding tissue, presence or absence of capsular preservation, and expression of Ki-67 have been reported as significant factors (P<0.05)[6]. Watanabe *et al*[9] reported that the 5-year recurrence rate of LGPA was 2.8% in Japan. In our suspected recurrent case (representative first case), the capsule could be well-preserved intraoperatively but MRI 3y after the surgery showed a mass on the dorsal superior surface of the left lacrimal gland. T2-WI showed a heterogeneous internal structure but no obvious multifocal lesions as typical findings of recurrence, so the patient was placed under observation at that time. If multifocal nodular lesions appear or the lesion tends to grow during observation, complete resection by orbitotomy would be immediately needed.

This study had some limitations. First, the average follow-up period was 6.58y, and local recurrence rates of tumors may increase with future extension of the follow-up period. Second, this study was conducted at two institutions in Hokkaido, Japan with a relatively small number of cases.

In conclusion, primary LGPA of the orbital lacrimal gland could complicate high IOP, and requires total tumor excision by means of orbitotomy. Rarely, systemic malignancy may complicate a lacrimal gland tumor that is suspected to be a pleomorphic adenoma, in which total removal of the lacrimal gland tumor should be considered at the initial surgery.

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