Jpn J Ophthalmol
DOI 10.1007/s10384-016-0451-3

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Clinico-radiological features of primary lacrimal gland pleomorphic adenoma: an analysis of 37 cases

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Received: 24 June 2015 / Accepted: 13 April 2016

Abstract
Purpose To present the radiological and clinical features of primary lacrimal gland pleomorphic adenoma (PLGPA).
Methods Thirty-seven consecutive PLGPAs presenting to two hospitals in Japan were reviewed.
Results PLGPA cases had 15 men and 22 women with a mean age of 51.9 years. Common presenting features were ptosis (83 %), diplopia (78 %) and globe displacement (78 %). Twenty-two percent of cases reported symptom duration of less than 6 months, but only 5.6 % of cases had pain. Sixteen percent of PLGPAs were centered in the palpebral lobe; none of which were associated with globe indentation or lacrimal fossa expansion. Bony excavation was observed in 84 % of orbital lobe PLGPA; the bone margin was well demarcated and the character of excavation was more frequently smooth than scalloped (2:1). The presence of globe indentation or bony excavation was associated with increased tumor size ($p = 0.003$). An enhancing rim was visible on T1-weighted fat-suppressed gadolinium-enhanced magnetic resonance imaging (T1FS-Gad MRI) in 27 %. Five (19 %) enclosed cystic spaces were bright on T2-weighted MRI and non-enhancing. Calcification of tumor parenchyma was common in cystic cases but rare in non-cystic cases ($p = 0.01$).
Conclusions PLGPAs have varied clinical and radiological features. Common radiological features are a heterogeneous internal architecture on T2-weighted MRI, an enhancing rim on T1FS-Gad MRI, smooth or scalloped bony excavation with intact cortical bone, and globe indentation. Cystic spaces, calcification, and symptom duration less than 6 months are common, but pain is rare. Awareness of the clinico-radiological variants of PLGPA is important when considering incisional biopsy of a lacrimal gland mass.

Keywords Pleomorphic adenoma · Lacrimal gland · Radiological variants

Introduction

Although some clinicians utilize pre- or intraoperative biopsies in the management of primary lacrimal gland pleomorphic adenoma (PLGPA), many believe that optimal management requires a strong presumptive diagnosis followed by excisional biopsy [1, 2]. Clinicians must be familiar with the radiological features of PLGPA when interpreting patient imaging and planning management. The preoperative diagnosis can be challenging because PLGPAs have varied imaging characteristics as a consequence of their heterogeneous histology. By definition, PLGPAs are composed of variable proportions of both epithelial and mesenchymal components. The mesenchymal component may include myxoid, chondroid, hyaline, mucinous or adipose tissue, resulting in a wide variety of radiological features.

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Published online: 16 May 2016

Radiological reviews of PLGPA are scarce and have either not reported magnetic resonance imaging (MRI) data [3], analyzed fewer than 4 cases [4–6], or are literature reviews that present index cases for illustration purposes only [7–9]. There are no published reports describing the computed tomography (CT) and MRI features of a large number of PLGPA cases. The purpose of this study was to characterize the radiological and clinical features of a large cohort of PLGPAs. Focus is placed on the radiological variants that have been under-reported in the literature to date.

Patients and methods

Patients

This study was a retrospective, twin-center, observational case series conducted in the Seirei Hamamatsu General Hospital, Shizuoka, Japan, and the Kyoto Prefectural University of Medicine, Kyoto, Japan. Cases of histologically confirmed PLGPA presenting between January 2004 and March 2012 were identified by searching the pathology archive of each institution. Tumors with foci of malignant transformation (carcinoma ex pleomorphic adenoma) were excluded. Institutional review board approval for this study was obtained.

Clinical information

Demographic information (gender, age), presenting features (lid swelling, diplopia, globe displacement, pain, symptom duration at time of first review by an ophthalmologist) and follow-up data (tumor recurrence, malignant transformation, duration of follow-up) were recorded.

Radiological review

The following imaging features of PLGPA were recorded: location (orbital or palpebral lobe), maximal dimension, borders (smooth, bosselated, poorly-defined), bony excavation on CT (none, smooth, scalloped), contrast enhancement on CT and MRI (none, homogeneous, heterogeneous), globe indentation (absent, present), visibility of a tumor capsule on CT and MRI (absent, present), internal architecture on CT and MRI (homogeneous, heterogeneous), and signal intensity on MRI. The signal intensity on T1-weighted MRI was compared to white matter (low, iso-intense, high) and the signal intensity on T2-weighted was classified as follows: bright signal (very high intensity) was defined as a signal intensity higher than that of cerebrospinal fluid (CSF), high intensity was between that of CSF and skeletal muscle, and low intensity was below that of skeletal muscle. Scalloped bony intensity was defined as two or more segments of curvilinear excavation meeting at a ridge.

Surgical technique

Pleomorphic adenomas were explored through an upper eyelid skin crease incision. A supero-lateral orbitotomy was performed for all orbital lobe tumors, with the exception of very small tumors whose posterior pole could be safely mobilized without the need for orbitotomy. The periosteum of the superior orbital rim was exposed, incised and stripped from the lacrimal fossa using blunt dissection. The supero-lateral orbital rim was then removed to improve access. The tumor was completely mobilized without the use of sharp instrumentation and removed intact on its sheet of orbital periosteum. The orbital rim was then replaced and the periosteum and soft tissues closed.

Results

Thirty-seven consecutive patients with histologically confirmed PLGPA were included in this study: 24 cases from Seirei Hamamatsu General Hospital and 13 cases from the Kyoto Prefectural University of Medicine. There were 15 men and 22 women, mean age was 51.9 years (range 24–91 years).

Radiological features

Imaging was available for all 37 cases. Twenty-seven cases had CT and MRI, seven cases had CT only and three cases had MRI only. The radiological features of primary LGPA are presented in Table 1.

Focality and dimensions

All PLGPAs were unifocal tumors, 16 % of which were centered in the palpebral lobe. The median maximal tumor dimension was 20 mm; 24 % of tumors were $\leq$10 mm, 5 % of tumors were >30 mm.

Bony change and globe indentation

No palpebral lobe tumors caused bony change or globe indentation. Of orbital lobe PLGPAs, 84 % caused lacrimal fossa expansion and 77 % indented the globe. Globe indentation appeared as deformity of the sclera on CT (Fig. 1a) and deformity of vitreous on T2-weighted MRI. For orbital lobe tumors, increased mean tumor diameter was associated with both lacrimal fossa expansion

Table 1 Radiological features of primary lacrimal gland pleomorphic adenoma

Parameter (cases for which parameter could be assessed)	Characteristic	$n = 37$ (%)
Imaging modality (37)	CT only	7 (19)
	MRI only	3 (8)
	CT and MRI	27 (73)
Location of tumor within lacrimal gland (37)	Orbital lobe	31 (84)
	Palpebral lobe	6 (16)
Maximal dimension of largest tumor (37)	0–10 mm	4 (11)
	11–15 mm	5 (13)
	16–20 mm	11 (30)
	21–25 mm	5 (13)
	26–30 mm	8 (22)
	31+ mm	4 (11)
Borders (34)	Smooth	26 (76)
	Bosselated	7 (21)
	Poorly defined	1 (3)
Globe indentation, orbital lobe tumors (31)	Present	24 (77)
	Absent	7 (23)
Character of lacrimal fossa expansion on CT, orbital lobe tumors (31)	None	5 (16)
	Smooth	20 (65)
	Scalloped	6 (19)
Enhancing rim around tumor on MRI (30)	Not visible	22 (73)
	Faintly visible	3 (10)
	Clearly visible	5 (17)
Tumor parenchyma calcification on CT (34)	Present	4 (12)
	Absent	30 (88)
Rim calcification on CT (32)	Present	2 (6)
	Absent	30 (94)
Contrast enhancement on CT and/or MRI (22)	None	0
	Homogeneous	10 (45)
	Heterogeneous	12 (55)
	Cerebriform	4
Internal features on CT (32)	Homogeneous	27 (84)
	Heterogeneous	5 (16)
	Cystic	3
Internal features on T1 sequence MRI (27)	Homogeneous	12 (44)
	Heterogeneous	15 (56)
Internal features on T2 sequence MRI (27)	Homogeneous	4 (15)
	Heterogeneous	23 (85)
	Cystic	5
T1 intensity relative to white matter (27)	Low	14 (52)
	Iso	10 (37)
	High	3 (81)
T2 intensity as described in methods (27)	Low	0
	High	23 (85)
	Bright	0
	Bright in high	4 (15)

($p = 0.003$) and globe indentation ($p = 0.003$). There was no significant association between the presence of lacrimal fossa expansion and other imaging characteristics such as bosselated tumor borders ($p = 0.56$), an enhancing rim on MRI ($p = 0.29$), cystic internal architecture on MRI ($p = 1.00$), or tumor calcification on CT ($p = 1.00$). In the

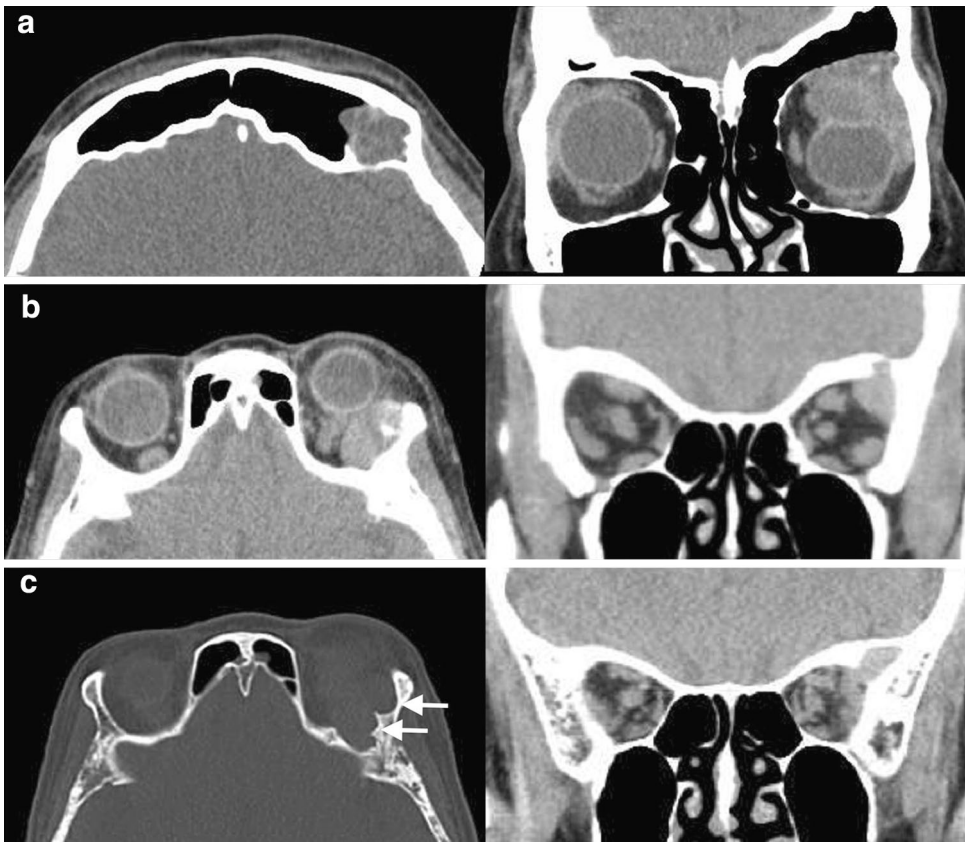

Fig. 1 Scalloping of the lacrimal fossa in PLGPA. **a** In addition to focal scalloping, this tumor demonstrates erosion of the orbital roof and indentation of the sclera. **b** Deep bony excavation of the orbital roof. Calcification of the tumor parenchyma is visible on the transverse image. MRI of this case demonstrated cystic change (not shown). **c** Recurrent lacrimal gland pleomorphic adenoma from case b, 71 months after incomplete excision from the bone margin. Scalloped bony excavation is well demonstrated on the transverse image (*arrows*)

majority of cases, the bony change was a smooth, shallow, diffuse expansion of the lacrimal fossa. Smooth bony excavation tended to be greatest in the superotemporal aspect of the lacrimal fossa, giving the lacrimal fossa a 'cornered' appearance on coronal reconstructions. Scalloped bony excavation was present in 19 % of cases and these excavations conformed to bosselations present on the tumor surface. Two PLPGAs were associated with narrow foci of deep bony excavation (Fig. 1a, b). All PLGPAs were well marginated at the bone-tumor interface and cortical bone was radiologically intact on CT.

Internal architecture

The internal architecture of PLGPA in over 80 % of cases was homogeneous on CT and heterogeneous on T2-weighted MRI. On T1, approximately half of PLGPAs were homogeneous and half were heterogeneous. One PLGPA was septated into two lobes. Five (19 %) PLGPAs enclosed well-defined spaces that, relative to the rest of the tumor, were hyperintense on T1-weighted MRI, bright on T2-weighted MRI, hypodense on CT, and non-enhancing. These imaging characteristics were consistent with a cyst filled with either proteinaceous material or hemorrhage. Histological correlation was available for three cystic cases and revealed cavities lined by hyaline connective tissue and squamous epithelium. One case contained necrotic material and hemorrhage, which appeared on imaging as dependent layering within the cyst. Parenchymal calcification was visible on CT in 12 % of cases; this included three of five cystic cases but only one of 22 non-cystic cases ($p = 0.01$) (Fig. 2). All PLGPAs enhanced with contrast; however, 55 % contained non-enhancing areas (heterogeneous enhancement). Four (18 %) cases had a 'cerebriform' appearance on gadolinium-enhanced MRI (Fig. 3).

Enhancing rim

A thin rim of enhancing tissue on T1 fat-suppressed gadolinium-enhanced (T1FS-Gad) MRI was visible in 27 % of PLGPAs. The rim was occasionally visible on CT as a hyperdense outline and it rarely contained specks of calcification.

Clinical features

Clinical data were available for 36 cases. The clinical features of PLGPA are presented in Table 2. There was 1 tumor recurrence (Fig. 1b, c) during a median follow-up of 55 months. This patient with recurrent tumor declined radical resection, instead opting for a debulking operation without bone excision, which was repeated 24 months

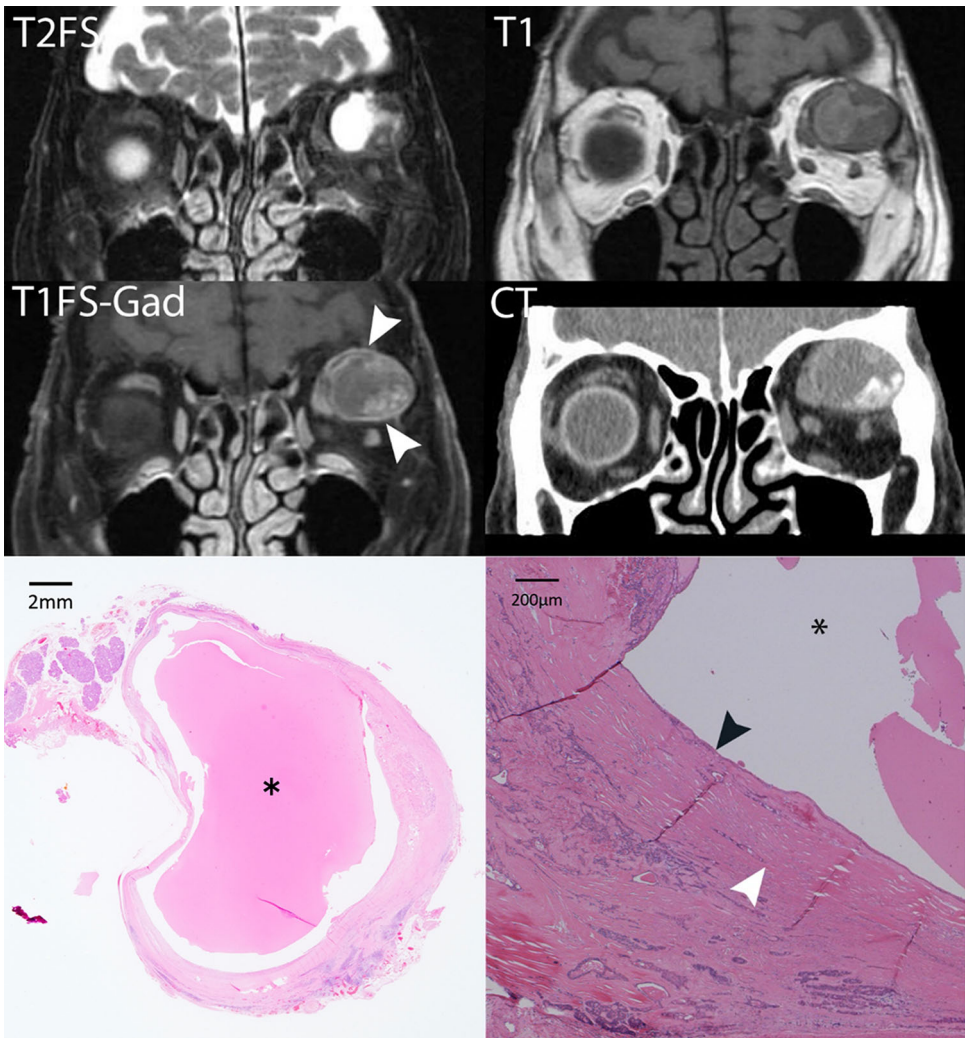

Fig. 2 Cystic PLGPA featuring parenchymal calcification and visible pseudocapsule T2 fat suppressed (T2FS) and T1-weighted MRI: a cystic space is visible with signal intensity that is bright on T2FS and iso-intense to white matter on T1, consistent with proteinaceous material. T1FS-Gad: the tumor has an enhancing rim (*white arrowheads*). The cystic space is non-enhancing. CT: there is calcification of the tumor parenchyma, most intense at the cyst-tumor interface (confirmed in axial slices, not shown). Hematoxylin and eosin staining reveals a large cystic space (*asterisk*) containing serous liquid and lined by simple squamous epithelium (*black arrowhead*). It is bordered by hyaline connective tissue (*white arrowhead*)

later. On both occasions the pathology showed pleomorphic adenoma without malignant change.

Discussion

The primary aim of this study was to characterize the radiological features of PLGPA with particular focus on the radiological variants that have been under-reported in the literature to date. Our findings demonstrate that PLGPAs present with a wide range of imaging features. Many of the imaging variants, while not uncommon, have only been reported rarely; yet several of these variants have historically been considered hallmarks of malignancy.

This is the largest published study reporting the CT and MRI features of PLGPA. Zeng and colleagues reviewed 213 PLGPAs; however, only 28 % of those cases were imaged with CT and less than 19 % were imaged with MRI [3]: unfortunately, no MRI data was reported. Rose and Wright presented basic CT data for 54 PLGPAs, but this imaging was obtained between 1975 and 1990 using early generation scanners [10]. Few radiological reviews of PLGPA have been published, and these have either analyzed fewer than 4 cases [4–6], or are literature reviews that present index cases for illustration purposes only [7–9].

A relatively high proportion (19 %) of PLGPAs featured cystic spaces on MRI. This imaging variant has been described in only a few case reports previously [5, 11–13]. Cysts were not reported at all in the large series of 213 pleomorphic adenomas by Zeng et al. [3], possibly because the authors did not review MRI data. In contrast, cystic spaces have frequently been reported in pleomorphic adenoma of the salivary glands [14]. We noted intertumoral variations in the T1 and T2 intensity of the cystic spaces, likely reflecting the variable proteinaceous or mucinous nature of these cysts. Cysts in our series were non-enhancing, consistent with fluid-filled avascular cavities. Previous reports describe trace enhancement of PLGPA cysts comprising cartilaginous and myxomatous tissue [5, 14, 15]. In other reports, PLGPA cysts resulted from

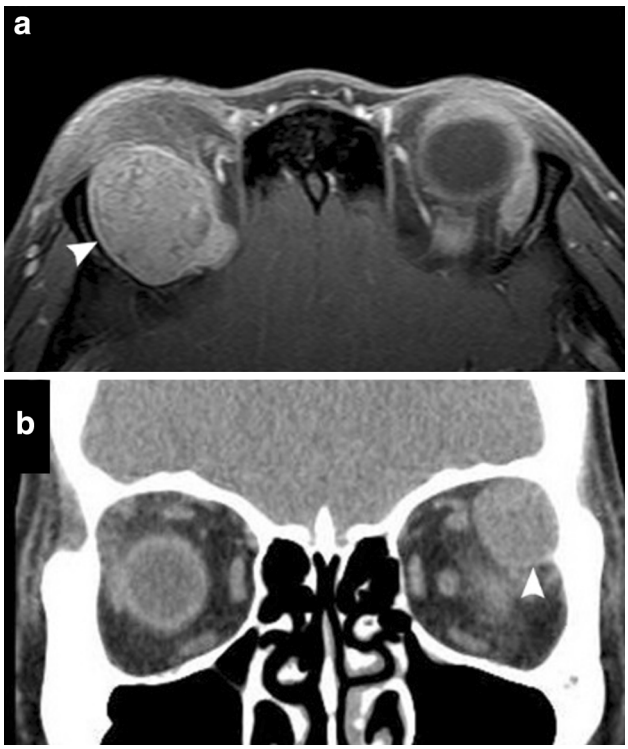

Fig. 3 Tumor encapsulation in PLGPA. **a** T1FS-Gad, circumferential rim enhancement of a PLGPA (*arrow*). The tumor avidly enhances and has a 'cerebriform' internal architecture. **b** PLGPA (from a different patient) has a hyperdense outline on non-contrast CT, most visible inferiorly (*arrowhead*)

Table 2 Clinical features of primary lacrimal gland pleomorphic adenoma

Parameter	$n = 36$
Male:female	2:3
Mean age, months (range)	51.9 (24–91)
Median duration of symptoms, months (range)	12 (1–96)
Symptom duration <6 months (%)	8 (22)
Orbital lobe tumors (%)	8
Palpebral lobe tumors (%)	0
Diplopia (%)	28 (78)
Ptosis (%)	30 (83)
Globe displacement (%)	28 (78)
Pain (%)	2 (5.6)
Recurrences (months after excision)	1 (71)
Malignant transformation	0
Median follow-up, months (range)	55 (4–97)

intratumoral hemorrhage [12, 13, 16]. Hematic PLGPA cysts contain liquefied and clotted blood products and may feature cholesterol granulomata in the cyst wall [16]. Pathological correlation was available for three of our cystic cases and revealed serous material, and in one case necrotic tissue and hemorrhage. The hemorrhage appeared on MRI as dependent layering, an imaging variant of PLGPA that has been described only once before [13]. Interestingly, three of our cystic cases were partially or completely lined by squamous epithelium. To the best of our knowledge, squamous epithelial lining of PLGPA cysts has not been previously described.

Lacrimal fossa expansion was present in 84 % of all orbital lobe PLGPAs and was significantly associated with increased tumor size ($p = 0.003$). By demonstrating a statistically significant relationship between PLGPA size and bone expansion, our results support the concept of pressure-induced lacrimal fossa remodeling in PLGPA. McNab and Satchi present interesting data that suggests a pressure-independent mechanism of bone remodeling in recurrent lacrimal gland pleomorphic adenoma (RLGPA) [17]. Two of our PLGPA cases featured narrow zones of deep bony excavation (Fig. 1a, b), an unusual appearance for PLGPA that could be consistent with a pressure-independent mechanism. However, the character of bony erosion in all other cases of PLGPA was in keeping with pressure-induced remodeling. Multinodular or bosselated tumors caused scalloped excavation, presumably due to uneven distribution of pressure along the bone face. Current literature gives the impression that multinodular growth and bony scalloping are relatively specific features of RLGPA. Five of five RLGPAs reported by McNab and Satchi [17], and three of three RLGPAs reported by Weis et al. [18] were multinodular and caused scalloped erosion. Although scalloped erosion was less frequent in our cohort of PLGPAs, it is important to note that it still occurred in 19 % of cases. Focal bony excavation in primary tumors should be noted preoperatively by surgeons as it has implications for complete tumor clearance.

PLGPAs featured calcification of both the tumor rim and the tumor parenchyma. Parenchymal calcification was visible on CT in 12 % of cases and was significantly more common in cystic tumors ($p = 0.01$). An association between cystic change and calcification has not been reported previously. Radiological evidence of parenchymal calcification in PLGPA was observed in 7 of 22 cases (32 %) by Rootman [19], but only 4 of 78 cases (5.1 %) reported by Rose and Wright [10], and 2 of 32 cases (6.3 %) reported by Sen et al. [11]. Histology reviews have found that scattered calcification may occur in areas of keratin and chondroid [20], whereas dense calcification may indicate osseous differentiation of the tumor [10].

An enhancing rim was observed in 30 % of PLGPAs and likely reflects the presence of a pseudocapsule, which is a well-described histological feature of PLGPA (Fig. 3) [21]. The pseudocapsule comprises adjacent compressed orbital tissue and reactive fibrosis. It ranges from a few micrometers to several hundred micrometers in thickness [18], which accounts for it being inconsistently visible on imaging. Rim calcification was visible in several of our

PLGPA cases, whereas this imaging feature has not been reported previously.

The clinical features of PLGPA in our cohort were consistent with the existing literature with the exceptions of a higher rate of diplopia (78 %) and, more notably, 22 % of cases reporting symptom duration of less than 6 months [10, 22, 23]. Surprisingly, all cases with a short duration of symptoms had tumors centered in the orbital lobe of the lacrimal gland. Rose and Wright found that 23 % of their 78 PLGPA cases had symptom durations of less than 8 months, but the majority of these tumors were centered in the palpebral lobe [10]. Palpebral lobe PLGPA accounted for 16 % of our cases and 12 % of the cases reported by Rose and Wright [10]. No other studies have calculated the proportion of PLGPA centered in the palpebral lobe. Of note, only two of our cases (5.7 %) complained of orbital pain. The reported prevalence of pain in PLGPA ranges 5.2–7.1 % [3, 22]. In contrast, pain has been reported to occur in 73–80 % of adenoid cystic carcinomas [24–26], 50 % of adenocarcinomas [24], and 33 % of malignant mixed tumors [24]. In a review of 298 lacrimal gland epithelial tumors, pain was significantly associated with malignancy ($p < 0.01$) [3].

Several clinical and radiological features can help to distinguish malignant and benign lacrimal gland tumors. Clinical features suggesting malignancy include pain, numbness in the distribution of the ophthalmic division of the trigeminal nerve, and a short duration of symptoms (although pleomorphic adenomas can also present with a short history). Radiological features suggesting malignancy include invasion of bone cortex, ill-defined tumor extension outside of the lacrimal gland, and molding around the globe.

In summary, PLGPAs present with a wide spectrum of clinico-radiological features. Cystic spaces, scalloped bony excavation, calcification, and symptom duration less than 6 months are not uncommon. Pain in PLGPA is rare. Awareness of the clinico-radiological variants of PLGPA has significance when considering biopsy of a lacrimal fossa mass lesion. In addition, the surgeon must be cognisant of areas of scalloped excavation when planning complete tumor excision.

Conflicts of interest A. Watanabe, None; N. H. Andrew, None; K. Ueda, None; S. Kinoshita, Consultant (Santen Pharmaceutical, Otsuka Pharmaceutical); N. Katori, None; M. Reid, None; A. Pirbhai, None; D. Selva, None.

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