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Differentiating intradiploic orbital dermoid and epidermoid cysts utilizing clinical features and machine learning

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Purpose: The purpose of this study was to characterize intradiploic dermoid and epidermoid orbital cysts to determine any differences in clinical, radiographic, or surgical features. **Methods:** A retrospective review was performed of patients presenting with intradiplopic dermoid or epidermoid cysts. Additionally, a complete review of the literature was performed to identify cases of intradiplopic orbital dermoid and epidermoid cysts. Data collected included age, sex, presenting symptoms, location of intradiplopic cyst, ophthalmic findings, treatment, and follow-up. Clinical features of dermoid versus epidermoid cyst were compared. Additionally, machine-learning algorithms were developed to predict histopathology based on clinical features. **Results:** There were 55 cases of orbital intradiploic cysts, 49 from literature review and six from our cohort. Approximately 31% had dermoid and 69% had epidermoid histopathology. Average age of patients with dermoid cysts was significantly lesser than that of patients with epidermoid cysts (23 vs. 35 years, respectively; $P = 0.048$). There was no difference between sex predilection, presenting symptoms, radiographic findings, or surgical treatment of dermoids and epidermoids. The majority of patients (64%) underwent craniotomy for surgical removal. Machine-learning algorithms KStar and Neural Network were able to distinguish dermoid from epidermoid with accuracies of 76.3% and 69%, respectively. **Conclusion:** Orbital intradiploic cysts are more commonly epidermoid in origin. Dermoid cysts presented in younger patients; however, there were no other significant differences in features including ophthalmic or radiographic findings. Despite similar features, machine learning was able to identify dermoid versus epidermoid with good accuracy. Future studies may examine the role of machine learning for clinical guidance as well as new surgical options for intervention.

Key words: Machine Learning, orbital dermoid, orbital tumor

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Orbital dermoid cysts – keratin-filled cyst lined by simple squamous epithelium and skin adnexal elements – and epidermoid cysts – cyst wall does not contain skin adnexal elements – are well-described benign tumors, commonly presenting in childhood as a palpable mass along the superotemporal orbit.[1] Deep orbital dermoid cysts are less common, often occurring later in life with headaches, proptosis, and signs of inflammation.[2] Less common still are intradiploic cysts involving the diploe of the sphenoid, frontal, or zygomatic bones of the orbit, which more frequently occur intracranially along the posterior fossa or cerebellopontine angle.[3,4] Patients with intradiploic orbital cysts may present with acute symptoms[5] or chronic changes including pain, headache, proptosis, or diplopia.[3] Intradiploic cysts involving the orbit include both dermoid and epidermoid histopathology, although no differentiating clinical features have been reported. Radiographically, dermoid cysts can contain fat and have a heterogenous signal on magnetic resonance imaging (MRI), while epidermoids can have densities closer to fluid, and therefore appear more homogenous with diffusion restriction. Intradiplopic cysts may be more difficult to treat than non-intradiploic cysts, which are often managed with orbitotomy.[2] Surgical treatment of intradiploic cysts often involves a craniotomy to remove the extent of the cyst due to the high risk of recurrence.[3]

Herein, the authors present six cases of intradiploic orbital cysts and perform a review of the literature to characterize the clinical and radiographic features, treatment, and recurrence rates of both dermoid and epidermoid cysts occurring within the diploe of orbital bones. Additionally, the authors compare the clinical features and outcomes of dermoid versus epidermoid histopathology.

Methods

This study was approved by the Institutional Review Board, and it adhered to the tenants of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. A retrospective case review was performed of intradiploic orbital dermoid or epidermoid cysts treated by the authors. Complete medical and ocular histories along with radiographic imaging of the brain and orbits were obtained for all patients prior to surgery. Additionally, a comprehensive literature

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review was performed to gather cases of intradiplopic orbital dermoid and epidermoid cysts. An electronic search strategy was used on the PubMed/MEDLINE database. Search terms included "orbital dermoid," "intradiploic," "orbital cyst," and "orbital epidermoid," with the logical operator "and." This search was conducted in December 2020. Individual case reports and case series were reviewed to determine whether each case represented an intradiploic cyst. Data collected included patient age, sex, presenting symptoms, ophthalmic exam, imaging characteristics, surgical management, histopathology, and follow-up. Patients and published reports were excluded if the orbital cyst was not intradiplopic or was not considered a dermoid or epidermoid cyst on histopathologic analysis.

Clinical features of dermoid versus epidermoid cysts were compared. Statistical analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using Student's *t*-test and categorical variables using Chi-square analysis. Univariable analyses were performed to evaluate which factors predicted possible dermoid versus epidermoid cysts. Weka (version 3.8.5) was utilized for machine learning, model creation, and model validation. The following six machine-learning algorithms were used: KStar, Multilayer Perceptron, Logistic Regression, Gradient Descent, Naïve Bayes, and Decision Tree. All models were evaluated using 10-fold cross validation. Weighted accuracy and Area under the curve- Receiver Operator Characteristic (AUC-ROC) were used to analyze model performance.

Results

A comprehensive review of the literature yielded 49 cases of intradiploic orbital dermoid or epidermoid cysts. In addition, six cases from the authors were added to this cohort. Of the 55 cases, approximately 31% were dermoid and 69% were epidermoid on histopathology. Average age of patients with dermoid cysts was significantly lesser than that of those with epidermoid cysts (23 vs. 35 years, respectively; $P = 0.048$). There was no difference between sex predilection of dermoids or epidermoids [Table 1]. Common presenting symptoms included proptosis, headache, diplopia, and externally visible findings such as swelling or ulcerated skin from draining sinus tracts or fistulas. In all six patients from our cohort, both computed tomography (CT) and MRI were obtained [Fig. 1]. In a review of the literature, CT was found to be the most described imaging modality. Radiographically, boney remodeling into the orbit or intracranial space was appreciated in close to 90% of all patients, while over 50% had mass effect into the orbit. Intracranial involvement was less commonly seen (23% in dermoid cysts and 18% in epidermoid cysts). The sphenoid (29%) followed by the frontal bone (18%) were the most common sites of intradiploic cysts. Of the six Mayo Clinic patients, radiology listed dermoid or epidermoid cyst as the diagnosis in five cases (83%). The majority of patients (64%) underwent extradural craniotomy, while orbitotomy was employed in 36%.

On univariable regression analysis, features associated with an increased odd of dermoid cysts included age (odds ratio [OR] 1.031, 95% confidence interval [CI] 0.999–1.064, $P = 0.05$). There were no other significant clinical or radiographic features that were predictive of dermoid or epidermoid cysts on regression analysis.

Table 1: Demographics of intradiploic orbital dermoid versus epidermoid cysts

	Dermoid (*n*=17)	Epidermoid (*n*=38)	*P*
Age (years)	23±20	35±20	0.048*
Sex (m)	9 (53%)	22 (40%)	0.732
Presenting symptoms			
Headache	3 (18%)	8 (21%)	0.770
Proptosis	7 (41%)	19 (50%)	0.545
Pain	1 (6%)	5 (13%)	0.424
Decreased vision	0 (0%)	2 (5%)	0.335
Diplopia	3 (18%)	5 (13%)	0.663
Globe displacement	1 (6%)	3 (8%)	0.791
External skin changes	7 (41%)	12 (32%)	0.489
Incidental finding	1 (6%)	5 (13%)	0.424
Radiographic findings			
Bony erosion	15 (88%)	34 (89%)	0.921
Mass effect into the orbit	9 (53%)	19 (50%)	0.848
Intracranial involvement	4 (23%)	7 (18%)	0.453
Boney involvement			
Sphenoid	5 (29%)	11 (29%)	0.684
Zygomatic	2 (12%)	2 (5%)	0.482
Frontal	3 (18%)	10 (36%)	0.244
Temporal	1 (6%)	1 (3%)	0.552
Ophthalmic findings			
Reduced vision	2 (12%)	9 (24%)	0.253
Abnormal extraocular motility	7 (41%)	10 (26%)	0.618
Proptosis	7 (41%)	19 (50%)	0.545
Surgery			
Craniotomy	7 (41%)	22 (40%)	0.251
Orbitotomy	7 (41%)	9 (24%)	0.187
Follow-up (years)	3.0±2.8	3.1±3.7	0.759

Table 2: Machine-learning classifiers to predict tumor histology

Classifier (10-fold -CV)	Accuracy	ROC
KStar	76.30%	0.746
Neural Network	69%	0.687
Logistic Regression	61.80%	0.634
Gradient Descent	65%	0.571
Naïve Bayes	69%	0.582
Decision Tree	63%	0.385

CV: Cross validation

Postsurgical complications were not documented in a majority of reports in the literature. Of the six cases at Mayo Clinic, vision remained excellent postoperatively, extraocular motility improved, and no complications were noted over an average 2.5 years (range 3 months–7 years) of follow-up. Over half of the patients (four/six) underwent MRI 3 months postoperatively, which showed complete resection of the cyst without any operative complications.

Utilizing data aggregated during the comprehensive literature search, machine-learning classifiers were developed

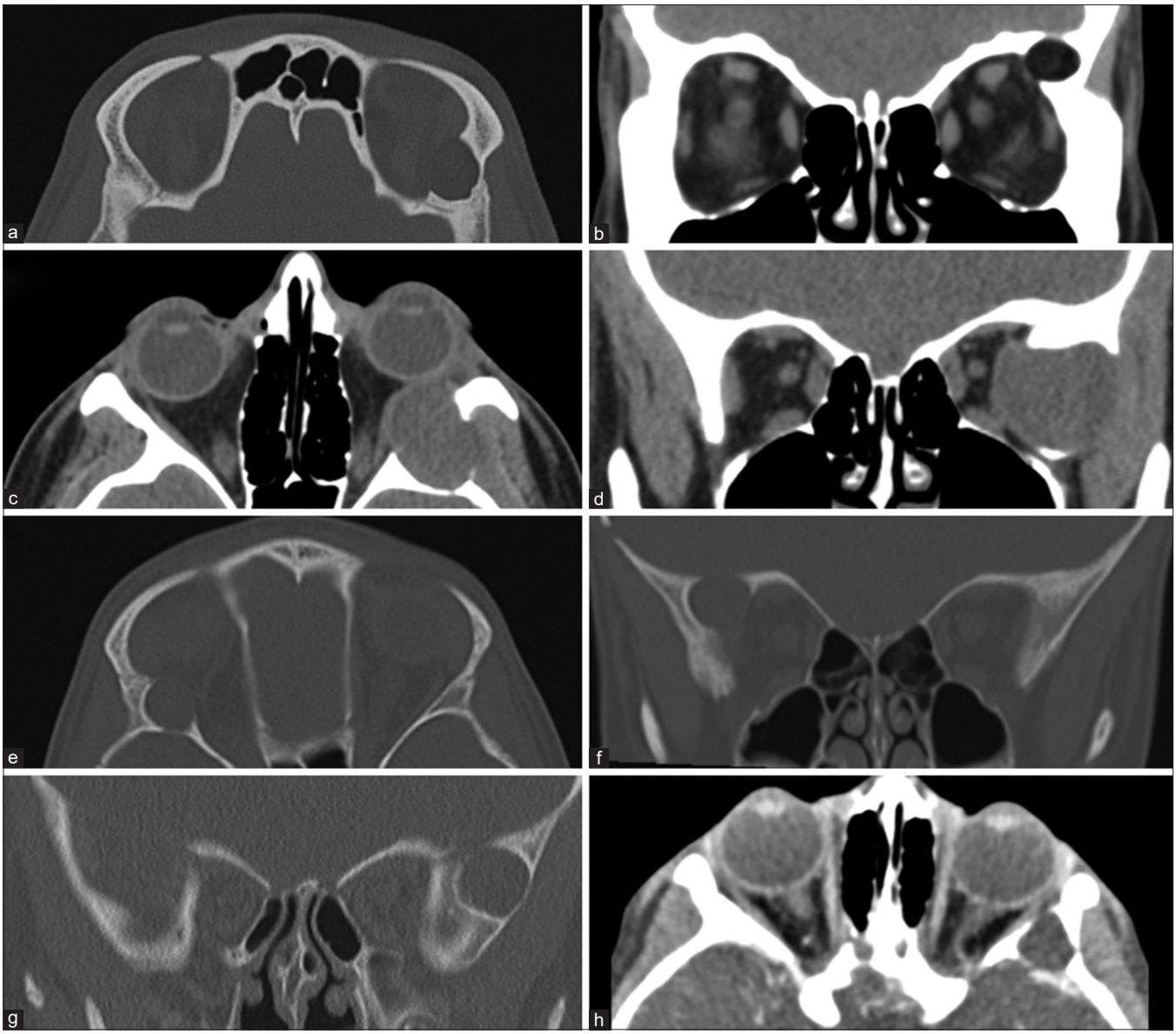

Figure 1: Intradiploic orbital dermoid and epidermoid cysts in Mayo Clinic patients treated with craniotomy. (a and b) Patient 1, note intradiploic orbital dermoid with osseous remodeling superiorly. (c and d) Patient 2, large intradiploic epidermoid cyst with orbital extension and mass effect on the globe. (e and f) Patient 3, intradiploic epidermoid cyst with osseous remodeling as well as mild mass effect on the lateral rectus muscle. (g and h) Patient 4, intradiploic epidermoid cyst with osseous remodeling superiorly

to predict tumor histologic classification. Age, sex, bone involved, motility changes, vision changes, proptosis >2 mm present, globe displacement, ptosis present, osseous changes on imaging, and mass effect on imaging were used as features to predict the tumor histological classification (dermoid vs. epidermoid). Two models had particularly strong performances (KStar and Neural Network with accuracies of 76.3% and 69%, respectively). Furthermore, AUC-ROC curves for both classifiers were 0.746 and 0.687, respectively [Table 2].

Discussion

Intradiplopic orbital dermoid and epidermoid cysts are rare, benign tumors, with only 49 cases reported in the literature.[3-51] Orbital dermoid cysts are far more common and are most often periocular, with several large series reporting over 80% presenting as a subcutaneous mass.[1,52] Deep orbital dermoid cysts, also referred to as endophytic cysts, have also been reported, and are more often present later in life with orbital inflammation.[2,53] These cysts, which may be dermoid or epidermoid, are rarely intradiploic in nature. Histopathologically, dermoid and epidermoid cysts are congenital rests from primitive ectoderm; dermoid cysts contain dermal and possible mesodermal elements, while epidermoids are composed completely of epithelium.[47] Despite these histopathological differences, the authors found the presentations, treatment, and recurrences of dermoid and epidermoid intradiploic orbital cysts to be nearly identical, with age being the only significant difference between groups. Given the failure of logistic regression and univariate analysis to identify unique factors between groups, we utilized

machine learning not for clinical classification, but to identify any multidimensional interactions across factors through prediction. Our machine-learning analysis showed that higher-order interactions are likely to occur across features that can distinguish between dermoid and epidermoid lesions. While at this time, preoperative differentiation of dermoid versus epidermoid cyst would likely not change the medical decision-making, machine learning demonstrates a difference, which may become clinically relevant over time as we encounter more of these cases.

While non-intradiploic deep orbital dermoids may present in similar fashion to intradiploic cysts, these may be managed by orbitotomy over craniotomy.[2] Intradiplopic cysts are more likely to involve the cranial space, and therefore, craniotomy is the most common treatment. With advances in surgical techniques, minimally invasive options may continue to expand. Nevertheless, the outcomes of craniotomy for intradiploic cyst removal are excellent, with no patients in the Mayo Clinic series suffering any complications related to surgery.

Traditional statistical analysis showed only age to be statistically significant between dermoids and epidermoids, although both may occur in younger patients. Radiology reads correctly identified dermoid/epidermoid histopathology 83% of the time, but does not consistently differentiate between the two. The accuracies of the top two machine-learning models to predict histology were unexpected, given the clinical and radiographic similarities. It is possible that statistical testing was underpowered, given the relatively low sample size due to the rarity of these tumors. The classifiers were chosen to represent the available demographics and clinical and radiographic features of the cases reported in the literature as well as the Mayo Clinic series. These models demonstrate that in a multidimensional feature space, there are distinct differences between dermoids and epidermoids. With additional cases, the characteristic differences between these two groups can be further elucidated, which is likely to improve the classification accuracy.

Limitations to this study include its retrospective nature, which relies on the accuracy of the medical record, as well as the inherent publication biases present in literature reviews. There was wide variability in the amount of clinical information, including the ocular exam and radiographic features, about the cases reported in the literature. Additionally, a case series of deep orbital dermoids likely included several intradiplopic cysts, but clinical information including cyst location was not provided for each individual case, therefore these were not included.[2] Regarding radiology interpretations, given the similar clinical presentations and treatments, radiologists have not historically prioritized differentiating between dermoid and epidermoid; therefore, we are unable to determine if the machine-learning algorithms would perform to the same level as trained radiologists, should emphasis be placed on distinguishing dermoid versus epidermoid histopathology. Complications were infrequently reported as well; however, in all six cases from Mayo Clinic, patients did very well without any postsurgical complications.

Conclusion

Intradiploic orbital dermoid and epidermoid cysts are rare benign tumors that often present with proptosis, diplopia, pain, or visible external changes including swelling, ulcerative lesions, or draining fistula tracts. While dermoid cysts are more common in younger patients, no other clinical or radiographic feature differentiates dermoid from epidermoid histopathology, and both lesions are successfully managed with craniotomy and/or orbitotomy. Machine-learning algorithms may allow us to further characterize intradiploic orbital cysts to aid in future diagnosis and treatment strategies. Further studies are needed to obtain more cases and to test tumor classification in a prospective manner.

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Conflicts of interest

There are no conflicts of interest.

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