Handout for IC 549: :AESTHETIC APPROACH TO OCULAR TUMORS

Topic : **Aesthetic approach to Ocular Tumors**
Chief Instructor: Dr Nupur Goel

Sub Topic : **Aesthetic Approach to Eyelid Tumors**
Instructor : Dr Nupur Goel

1. What is the primary goal of eyelid tumor management?
A) Cure the tumor
B) Preserve vision
C) Achieve good cosmesis
D) All of the above

✅ Answer: D) All of the above
The primary goal is to cure the tumor, preserve vision and eyelid function, and achieve good cosmesis. A multidisciplinary approach is often needed. Prioritizing goals depends on tumor type and location.

2. Which of the following eyelid tumors is most likely to be malignant?
A) Seborrheic keratosis
B) Basal cell carcinoma
C) Chalazion
D) Xanthelasma

✅ Answer: B) Basal cell carcinoma
Basal cell carcinoma is the most common malignant eyelid tumor. It's often seen in older adults, commonly at the lower eyelid margin. It's usually curable with surgery.

3. What is the preferred biopsy technique for suspected eyelid malignancy?
A) Excisional biopsy
B) Incisional biopsy
C) Shave biopsy
D) Punch biopsy

✅ Answer: B) Incisional biopsy
Incisional biopsy is preferred for suspected malignancy, providing tissue for histopathology. It's often done when tumor size or location makes excision difficult. Shave biopsy may be used for small, superficial lesions.

4. Which of the following is a reconstructive option for large upper eyelid defects?
A) Hughes flap
B) Cutler-Beard flap
C) Tenzel flap
D) Free skin graft

✅ Answer: B) Cutler-Beard flap
Cutler-Beard flap is used for large upper eyelid defects, using lower eyelid tissue. It's a two-stage procedure, providing good functional and aesthetic outcomes. Tenzel flap is another option for eyelid reconstruction.

5. What is the main advantage of Mohs surgery in eyelid tumor management?
A) Tissue conservation
B) Rapid healing
C) Minimal scarring
D) All of the above

✅ Answer: D) All of the above
Mohs surgery offers tissue conservation, rapid healing, and minimal scarring. It's useful for tumors with high recurrence risk or in cosmetically sensitive areas. It involves sequential excision and histological examination.

6. Which eyelid tumor is most likely to require orbital exenteration?
A) Sebaceous gland carcinoma
B) Basal cell carcinoma
C) Squamous cell carcinoma
D) Melanoma

✅ Answer: A) Sebaceous gland carcinoma
Sebaceous gland carcinoma is aggressive, with high recurrence and metastasis risk. Orbital exenteration may be needed for advanced disease or pagetoid spread. It's often misdiagnosed, leading to delayed treatment.

7. How should eyelid margins be reconstructed?
A) With skin grafts
B) With conjunctival flaps
C) With tarsoconjunctival flaps
D) With a combination of above

✅ Answer: D) With a combination of above

Eyelid margin reconstruction often involves combining techniques, like tarsoconjunctival flaps and skin grafts or flaps. The goal is to restore anatomy and function. Surgeon's skill and experience play a key role.

8. What is the role of sentinel lymph node biopsy in eyelid tumors?
A) Staging
B) Prognosis
C) Guiding adjuvant therapy
D) All of the above

✅ Answer: D) All of the above
Sentinel lymph node biopsy helps with staging, prognosis, and guiding adjuvant therapy. It's used for tumors with high metastasis risk, like melanoma or sebaceous gland carcinoma. It identifies patients needing further treatment.

9. Which of the following is a complication of eyelid tumor excision?
A) Ectropion
B) Entropion
C) Lagophthalmos
D) All of the above

✅ Answer: D) All of the above
Complications include ectropion, entropion, lagophthalmos, and others like scarring or eyelid malposition. Careful surgical planning and technique minimize risks. Post-op care is crucial.

10. What is the most important factor in determining the aesthetic outcome of eyelid tumor surgery?
A) Tumor size
B) Location of tumor
C) Reconstructive technique
D) Surgeon's skill

✅ Answer: D) Surgeon's skill
The surgeon's skill and experience are crucial for good aesthetic outcomes. They influence choice of technique, tissue handling, and closure. Tumor size and location also impact results.

Sub-topic: Aesthetic Approach to OCULAR SURFACE TUMORS- Dr Puneet Jain

1. What is the primary goal of managing ocular surface tumors?
A) Cure the tumor
B) Preserve vision
C) Achieve good cosmesis
D) All of the above

✅ Answer: D) All of the above

The primary goal is to cure the tumor, preserve vision, and achieve good cosmesis. A multidisciplinary approach is often needed, balancing tumor removal with preserving ocular function and appearance. Prioritizing goals depends on tumor type and location.

2. Which ocular surface tumor is most likely to be malignant?
A) Pterygium
B) Pinguecula
C) Conjunctival melanoma
D) Squamous papilloma

✅ Answer: C) Conjunctival melanoma

Conjunctival melanoma is a rare but aggressive malignancy. It often arises from primary acquired melanosis and has a high recurrence and metastasis risk. Early diagnosis and treatment are crucial.

3. What is the preferred biopsy technique for suspected ocular surface malignancy?
A) Excisional biopsy
B) Incisional biopsy
C) Fine-needle aspiration biopsy
D) none of the above

✅ Answer: D) NONE OF THE ABOVE
The choice depends on the size of the tumor and the differential diagnosis. For example, a small excisable OSSN needs an excision biopsy, whereas a large suspected conjunctival lymphoma needs an incisional biopsy. The term shave biopsy is generally used for eyelid tumors.

4. Which of the following is a treatment option for ocular surface squamous neoplasia (OSSN)?
A) Topical chemotherapy
B) Surgical excision
C) Cryotherapy
D) All of the above

✅ Answer: D) All of the above
Treatment options for OSSN include topical therapy (e.g.IFN, MMC), surgical excision, and cryotherapy. Combination therapy is often used, depending on tumor size and location.

5. What is the role of amniotic membrane transplantation in ocular surface tumor management?
A) To promote healing
B) To reduce inflammation
C) To reconstruct the ocular surface
D) All of the above

✅ Answer: D) All of the above
Amniotic membrane transplantation promotes healing, reduces inflammation, and reconstructs the ocular surface. It's often used after tumor excision or in cases with significant surface damage.

6. Which ocular surface tumor is associated with human papillomavirus (HPV)?
A) Conjunctival melanoma
B) Squamous cell carcinoma
C) Sebaceous gland carcinoma
D) Lymphoma

✅ Answer: B) Squamous cell carcinoma
HPV is associated with some cases of ocular surface squamous cell carcinoma. Other risk factors include UV exposure and immunosuppression. HPV types 16 and 18 are commonly implicated.

7. What is the main advantage of topical chemotherapy for ocular surface tumors?
A) Tissue conservation
B) Reduced scarring
C) Targeted treatment
D) All of the above

✅ Answer: D) All of the above
Topical chemotherapy offers tissue conservation, reduced scarring, and targeted treatment. It's often used for OSSN or as adjuvant therapy. Common agents include mitomycin C and 5-fluorouracil.

8. Which of the following is a complication of ocular surface tumor surgery?
A) Limbal stem cell deficiency
B) Corneal scarring
C) Conjunctival scarring
D) All of the above

✅ Answer: D) All of the above
Complications include limbal stem cell deficiency, corneal scarring, and conjunctival scarring. Careful surgical technique and post-op care minimize risks. Amniotic membrane grafts may help reduce scarring.

9. What is the role of cryotherapy in ocular surface tumor management?
A) To destroy tumor cells
B) To reduce tumor size
C) To treat residual tumor
D) All of the above

✅ Answer: D) All of the above
Cryotherapy destroys tumor cells, reduces tumor size, and treats residual tumor. It's often used as adjuvant therapy for OSSN or conjunctival melanoma. Freezing temperatures cause cellular damage and necrosis.

10. Which ocular surface lesion has a highest recurrence risk?
A) Pinguecula
B) Conjunctival melanoma
C) Squamous papilloma
D) Pterygium

✅ Answer: B) Conjunctival melanoma
Conjunctival melanoma has highest risk of local recurrence amongst the given options (in addition to local and systemic spread)

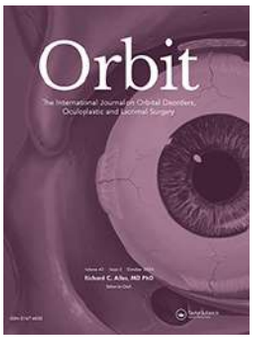
Sub-topic: Approach to intra-ocular tumours- Dr Sruthi.R.S

Intraocular tumours are broadly classified as primary or secondary (metastatic). Common examples include Retinoblastoma in children and Uveal melanoma in adults.
Management depends on tumour type, size, location, visual potential, and systemic status.

The main approaches include:

1. Observation – Small, indolent lesions (Eg: small choroidal nevi) may be monitored with serial imaging.
2. Laser therapy – Includes transpupillary thermotherapy (TTT) and laser photocoagulation, mainly for small tumours or adjunctive use.
3. Cryotherapy – Used for peripheral retinal tumours.
4. Radiotherapy –
   - Plaque brachytherapy (Eg: iodine-125) is commonly used for medium-sized uveal melanomas.
   - External beam radiotherapy, including proton beam therapy, is used in selected cases.
5. Chemotherapy – Systemic, intra-arterial, or intravitreal chemotherapy is especially important in retinoblastoma management.
6. Surgical management –
   - Local resection (iridectomy, iridocyclectomy, endoresection) in selected cases.
   - Enucleation for large tumours, painful blind eyes, or when globe salvage is not feasible.

Multidisciplinary care and regular systemic evaluation are essential, particularly in metastatic disease. The goal is life salvage first, then globe salvage, and finally vision preservation.



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REVIEW ARTICLE

Targeted therapy and immunotherapy for orbital and periorbital tumors: a major review

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ABSTRACT

Traditionally, for patients who are poor candidates for surgery and/or radiotherapy, palliative chemotherapy is often offered but with significant toxic side effects. However, recent advancements in our understanding of tumor biology and molecular genetics have brought new understanding to the molecular pathways of certain tumors and cancers. This has ushered in a new era of precision medicine specific to a tumor or cancer treatment pathway (targeted therapy) or directed to host-tumor responses (immunotherapy). This article will focus on recent updates in the application of available targeted and immunotherapy for managing orbital and periorbital tumors and tumor-like conditions, which include cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, cutaneous melanoma, Merkel cell carcinoma, sebaceous gland carcinoma, solitary fibrous tumor, dermatofibrosarcoma protuberans, orbital meningioma, neurofibromatosis, Langerhans cell histiocytosis, ocular adnexal lymphoma, orbital lymphatic malformation, and adenoid cystic carcinoma.

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Introduction

While the mainstay of management for orbital and periorbital tumors is usually surgery and/or radiotherapy,[1–3] in some instances, these tumors and tumor-like conditions can be locally aggressive and even metastasize.[4–7] Chemotherapy is often used as adjuvant therapy following surgical management, sometimes as a palliative measure. More recently, for patients who are not good candidates for surgery and/or radiotherapy, targeted and immunotherapy are now emerging as reasonable options and gaining traction for the management of patients with unresectable locally aggressive and metastatic tumors.[4,8]

Targeted therapy works by using agents or drugs that target a specific protein involved in a molecular pathway that is responsible for a specific cancer's survival and growth.[9,10] This, in theory, avoids the systemic toxicity of chemotherapeutic drugs. Thus, they are usually suitable for patients who are otherwise poor candidates for systemic chemotherapy.[4]

Conversely, ***immunotherapy*** works either by using the patient's immune system or laboratory-made substances to combat the immune evasion (host-tumor responses) of tumor cells. Examples include monoclonal antibodies, checkpoint inhibitors, or even cancer vaccines.[11] The goal of immunotherapy is to provide a specific and adaptive immune response necessary to achieve durable tumor regression and possibly cure.[12]

As with other tumours and cancers of the human body, tumors and tumor-like conditions can develop in the ocular adnexa, which includes the eyelids and periocular soft tissues, the orbit, and the lacrimal drainage system, similar to other types of cancer in the human body. In this review, we examine targeted and immunotherapy drugs that are relevant for treating periocular and periorbital tumors and tumor-like conditions.

Methods

In preparation for a major review, a comprehensive literature search was performed on PubMed and Google Scholar to identify studies and trials related to targeted and immunotherapy medications for periocular and orbital tumors from January 2005 to December of 2022. The search terms and keywords included but were not limited to the following: targeted therapy, immunotherapy, eyelid, lacrimal, orbit periocular, basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma, sebaceous gland carcinoma, cutaneous melanoma, ocular melanoma, meningioma, solitary

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fibrous tumor, dermatofibrosarcoma, and lymphoma. The titles and abstracts of the articles were reviewed for eligibility and screened for inclusion and exclusion criteria. Inclusion criteria included scientific and research articles (case reports, case series, clinical trials, randomized prospective studies, and systematic reviews) of drugs with results that have either equivalent or better objective response rate, median overall survival, or progression-free survival than current chemotherapy drugs of their respective diseases. Clinical trials of drugs that demonstrated poor objective response rates, median overall survival, or progression-free survival, or drugs that were discontinued were excluded.

Results

We conducted a literature search over 6 months and identified 101 studies related to the topic. Of these, 41 studies were deemed significant. From this subset, we found currently available targeted and immunotherapy options for 13 different tumor or tumor-like conditions affecting the periocular and orbital region. These tumors included cutaneous basal cell carcinoma (BCC) (vismodegib, sonidegib, cemiplimab), cutaneous squamous cell carcinoma (SCC) (erlotinib, cetuximab, pembrolizumab, cemiplimab), cutaneous melanoma (vemurafenib, dabrafenib, ipilimumab, pembrolizumab, nivolumab, trametinib, cobimetinib, encorafenib, binimetinib), Merkel cell carcinoma (MCC) (avelumab, pembrolizumab, nivolumab), sebaceous gland carcinoma (SGC) (pembrolizumab), solitary fibrous tumor (SFT) (sunitinib, sorafenib, pazopanib, axitinib), dermatofibrosarcoma protuberans (imatinib), orbital meningioma (everolimus and octreotide), neurofibromatosis (NF) (selumetinib), Langerhans cell histiocytosis (LCH) (vemurafenib, dabrafenib), ocular adnexal lymphoma (ibrutinib, rituximab), orbital lymphatic malformation (sirolimus), and adenoid cystic carcinoma (lenvatinib).

Discussion

We herewith provide a major up-to-date review of common ocular adnexal tumor and tumor-like conditions and an update on the mechanisms, principles, and concepts, and applications of current targeted and immunotherapy agents in use. The list of both targeted and immunotherapy drugs is summarized in Table 1. While there are distinct advantages compared to conventional management, occasionally unusual and atypical side effects, sometimes idiosyncratic may also be encountered, which are highlighted in Table 2.

Eyelid & periocular malignancies

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common skin cancer worldwide,[13] accounting for 90% of eyelid malignancies.[14] Management of BCC is typically by margin-controlled surgical excision, which is generally successful in a vast majority of patients.[15] However, for up to 10%, BCC tends to be locally aggressive and, in rare cases, metastasize.[16] For such patients, a weaker alternative was palliative cytotoxic chemotherapy,[13]

Table 1. Summary of current targeted and immunotherapy drugs for periocular and periorbital tumors.

Disease	Targeted Therapy	Immunotherapy	Combination Therapy	Only as Adjuvant
cBCC	Vismodegib, Sonidegib, Patidegib*, Itraconazole*	Cemiplimab		
cSCC		Pembrolizumab* Cemiplimab		Cetuximab*
cMelanoma	Vemurafenib, Dabrafenib	Ipilimumab, Pembrolizumab, Nivolumab	Dabrafenib + Trametinib, Vemurafenib + Cobimetinib, Encorafenib + Binimetinib	
Merkel Cell Carcinoma		Avelumab, Pembrolizumab, Nivolumab		
Sebaceous Gland Carcinoma		Pembrolizumab*		
Solitary Fibrous Tumour	Sunitinib*, Sorafenib*, Pazopanib*, Axitinib*			
Dermatofibrosarcoma Protuberans	Imatinib			
Meningioma	Sunitinib*, Apatinib*, Bevacizumab*		Everolimus + Octreotide*	
Neurofibromatosis	Selumetinib			
Langerhans Cell Histiocytosis	Vemurafenib*, Dabrafenib*			
Ocular Adnexal Lymphoma	Ibrutinib	Rituximab		
Orbital Lymphatic Malformation	Sirolimus*			
Adenoid Cystic Carcinoma	Lenvatinib*			

*Not FDA approved, currently investigated, or shows promise.

Table 2. Summary of adverse events related to targeted and immunotherapy drugs for periocular and periorbital tumors.

Disease	Drug	Noted Common Adverse Events	Ocular If Any
cBCC	Vismodegib	Muscle spasms, Alopecia, Dysgeusia, Weight decrease, Fatigue	
	Sonidegib	Muscle spasms, Alopecia, Dysgeusia, Nausea, Blood creatine Kinase Increase	
	Cemiplimab	Anemia, Nausea, Vomiting	Conjunctivitis, Dry eyes, Ocular Myesthenia
cSCC	Erlotinib	Rash, Fatigue, Stomatitis	
	Cetuximab	Fatigue, Anorexia, Constipation, Nausea	
	Pembrolizumab	Fatigue, pruritus	Anterior uveitis, Graves-like and myasthenia-like orbital disease
cMelanoma	Vemurafenib, Dabrafenib	Arthralgia, Rash, Fatigue, Hyperkeratosis	
	Ipilimumab	Diarrhea, pruritus, rashes, increase liver ALT and AST	Anterior uveitis, Facial nerve palsy, Giant cell arteritis
	Trametinib, Cobimetinib, Encorafenib, Binimetinib	Diarrhea, Arthralgia, Rash, Hyperkeratosis	
Merkel Cell Carcinoma	Avelumab	Fatigue, Fever and Chills	
	Pembrolizumab	Fatigue, pruritus	Anterior uveitis, Graves-like and myasthenia-like orbital disease
	Nivolumab	Rashes, Diarrhea, Vitiligo	Anterior Uveitis, Graves-like orbital disease
Sebaceous Gland Carcinoma	Pembrolizumab	Fatigue, pruritus	Anterior uveitis, Graves-like and myasthenia-like orbital disease
Solitary Fibrous Tumour	Pazopanib	Neutropenia, Anemia, Diarrhea	
	Axitinib	Fatigue, Hypertension, Mucositis	
Dermatofibrosarcoma Protuberans	Imatinib	Rashes, Fever, Muscle cramps, Abdominal pain	
Meningioma	Octreotide and Everolimus	Stomatitis, Fatigue, Diarrhea, Rashes	
	Sunitinib	Leukopenia, Fatigue, Thrombocytopenia, Diarrhea	
Neurofibromatosis	Selumetinib	Acne, Paronychia, Diarrhea, Irritability	
Langerhans Cell Histiocytosis	Vemurafenib, Dabrafenib	Arthralgia, Rash, Fatigue, Hyperkeratosis	
Ocular Adnexal Lymphoma	Rituximab	Neutropenia, Diarrhea, Constipation	
	Ibrutinib	Bleeding, Cardiac disease, Rash, Fatigue	
Orbital Lymphatic Malformation	Sirolimus	Bone marrow toxicity, Elevated triglyceride and cholesterol, Hypertension, Rashes	
Adenoid Cystic Carcinoma	Lenvatinib	Hypertension, Oral Pain	

however, with limited benefit and potential systemic toxicity[17] and thus justifying alternative therapies.

Targeted therapy in periocular BCC. Genomic studies in the majority of BCCs have identified a mutation in the Patched-1 gene (PTCH1) or Smoothened gene (SMO) of the Sonic Hedgehog signaling pathway (SHH).[14,18] In normal instances, PTCH1 acts as a receptor for SHH family signaling molecules, inhibiting SMO and its downstream expression.[19] Mutation in the PTCH1 gene, which is present in 70–90% of BCCs, activates the SMO gene, leading to the downstream activation of glioma-associated oncogenes (GLI), which lead to various cancers.[14,20]

Vismodegib. Vismodegib was the first-in-class approved targeted therapeutic drug for locally advanced and metastatic BCC. It selectively binds and inhibits SMO, thereby preventing downstream expression of genes in the SHH pathway that leads to cancers.[8,21] Landmark trials that tested the efficacy of vismodegib use in BCC include ERIVANCE, STEVIE, and EAS.

In ERIVANCE BCC trial, which evaluated patients with locally advanced and metastatic BCC, patients were given oral vismodegib (150 mg/day) until disease progression or intolerable toxicity.[22] Long-term investigator-assessed Objective Response Rate (ORR) was 48.5% in the metastatic BCC group (all partial responses) and 60.3% in the locally advanced BCC group (20 patients had a complete response, 18 had a partial response). The most common treatment-emergent adverse events include muscle spasms, alopecia, dysgeusia, and a decrease in weight.[22] ERIVANCE BCC trial showed durable responses and efficacy across all patient subgroups, including aggressive histologic types.[22] It is to be noted that in ERIVANCE trial that median overall survival (OS) was 33.4 months with Vismodegib, a vast improvement from the historical median survival of 8 months from systemic chemotherapy, though worth noting that these studies were not specific to periorbital disease, but such cases were included. [21]

STEVIE trial, the largest Vismodegib trial to date, also showed closely similar ORRs to the ERIVANCE trial. Investigator-assessed ORRs showed 68.5% for locally advanced BCC and 36.9% for metastatic BCC.[23] The stud y also demonstrated that the drug is tolerable in patients seen in clinical practice.[23] Moreover, when subgroup

analysis was made for patients with periocular locally advanced BCC, 28.7% achieved complete response, and 38.5% achieved a partial response, although some patients with complete response ultimately required additional therapy.[24] Treatment-emergent adverse events for STEVIE are closely similar to ERIVANCE, which include muscle spasms, alopecia, dysgeusia, and weight loss. Discontinuation was not uncommon in STEVIE trial due to adverse events. One patient ultimately developed treatment-related fatal hepatotoxicity. Secondary analysis showed that the drug also greatly improved health-related quality of life of studied patients.[25]

The Expanded Access Study (EAS) also evaluated oral 150 mg vismodegib for advanced BCC. The study showed ORRs of 46.4% for locally advanced BCC and 30.8% for metastatic BCC. This is lower than the results of ERIVANCE and STEVIE. EAS, however, demonstrated that the response was negatively associated with prior systemic chemotherapy.[26]

VISORB trial, on the other hand, evaluated vision-related outcomes specifically for orbital and extensive periocular BCCs. VISORB trial showed a reduction in the size of orbital and periocular BCCs to 44% of the baseline size in 3 months and 22% of the baseline size in 6 months while preserving globe and visual function in these patients.[27] The most common treatment-related adverse event for VISORB is dysgeusia, followed by myalgia and alopecia.[27]

Sonidegib. Sonidegib is a newer SMO antagonist approved by FDA for use of locally advanced and metastatic BCC. Unlike vismodegib, higher doses of sonidegib translate into increased drug levels in plasma with a sixfold increase in drug concentration in the skin compared to vismodegib.[28] This prompted the BOLT trial, which compared 200 mg vs. 800 mg once daily oral dose of sonidegib.[29] The study showed better ORR for locally advanced BCC for 200 mg dose at 56.1%, vs. 46.1% for the 800 mg dose. Fewer adverse events were also noted on the 200 mg dose compared to the 800 mg dose. For metastatic BCC, however, the 800 mg dose of sonidegib showed better ORR at 17.4% vs. 7.7% for the 200 mg dose.[29] Adverse events noted in the BOLT trial were reduced with a dosage of 200 mg of sonidegib compared to 800 mg. The most common adverse events included muscle spasms, hair loss, dysgeusia, and elevated creatine kinase levels.[29]

Patidegib and Itraconazole. Patidegib is a topical targeted therapeutic agent that exhibits its effect by inhibiting SMO of the SHH pathway.[30] A phase II clinical trial evaluating the efficacy and safety of 2% and 4% patidegib gel was compared to vehicle gel in patients with Gorlin Syndrome with Stage 1 BCC. At 26 weeks, patidegib 2% demonstrated a 51.29% reduction in the number of tumors from baseline vs. only 26.63% with 4% patidegib, demonstrating better clinical effects and fewer adverse effects for 2% patidegib.[30] Recently, itraconazole, a widely used antifungal drug, has been studied for its ability to inhibit the SMO protein and, thus, its inhibitory effects on the SHH pathway.[31] One Phase II trial of itraconazole demonstrated a reduction of the SHH pathway by 65% and a reduction in the tumor by 24%.[32]

Immunotherapy in periocular BCC.

Cemiplimab and Pembrolizumab. Cemiplimab was the first immunotherapeutic drug approved by FDA.[33] Phase II trial of Cemiplimab 350 mg performed in 84 patients intolerant or unresponsive to Hedgehog Inhibitors (vismodegib, sonidegib) after 9 months of treatment showed an ORR of 31%.[34] Among the adverse events observed in patients, the most common ones were hypertension and colitis, with each being reported in 5% of cases.[34] Additionally, ocular side effects related to cemiplimab include conjunctivitis, dry eyes, ocular myasthenia, and diplopia.[35] Pembrolizumab was similarly used in small case series for patients intolerant or unresponsive to Hedgehog inhibitors, which also show promise.[36,37]

Summary: Vismodegib, sonidegib, and cemiplimab have good clinical outcomes and safety profiles for patients with locally advanced and metastatic cBCC and may be a good option for patients who are not good candidates for surgery and/or chemotherapy.

Squamous cell carcinoma

Periocular cutaneous squamous cell carcinoma (cSCC) is the second most common eyelid malignancy.[38] While the mainstay management is surgical resection,[38] for locally advanced and metastatic cases, chemotherapy and radiotherapy have been the standard.[39,40] Overexpression of Epidermal Growth Factor Receptor (EGFR) is found in 90% of cSCC, and its presence indicates a negative prognostic factor.[41] However, *current* evidence for monotherapy with either a targeted or an immunotherapy drug for cSCC demonstrates weak activity.[42] For this reason, available targeted and immunotherapy agents are usually paired with either chemotherapy or radiotherapy.

Immunotherapy in periocular SCC.

Cetuximab. Cetuximab is a recombinant human murine immunoglobulin G1 antibody that binds to the extracellular domains of EGFR, inhibiting its activation.[43] However, in most studies, cetuximab was given as an adjunct to chemotherapy and/or radiotherapy.[42,44–46] The

EXTREME study was the first to evaluate the addition of cetuximab to the accepted protocol of cisplatin/carboplatin and fluorouracil, which showed that the addition of cetuximab increased OS (10.1 months vs 7.4 months) and ORR (36% compared to 20% with platinum-fluorouracil alone).[44] Similar positive results were seen when cetuximab was added to docetaxel and cisplatin in the GORTEC study, where the addition of cetuximab had an ORR of 44.4% and an OS of 14 months.[45]

Pembrolizumab. Pembrolizumab acts by targeting Programmed Cell Death receptor-1 (PD-1), thereby reactivating T-cell response against tumor cells.[47] KEYNOTE-629[48] was a phase II trial that investigated the use of pembrolizumab as monotherapy for recurrent or metastatic cutaneous SCC. The trial demonstrated an ORR of 34.3% and median progression-free survival (PFS) of 6.9 months.[48] Pembrolizumab was also studied as a first-line single drug for unresectable cutaneous squamous cell carcinoma in the CARSKIN trial,[49] which also evaluated patients based on PD-L1 expression. The overall response rate to pembrolizumab was 42%, with a median OS of 25.3 months. The trial also showed that PD-L1 expression appears to be predictive of pembrolizumab effectivity.[49]

Cemiplimab. Cemiplimab is a PD-1 inhibitor recently approved by FDA for patients with locally advanced or metastatic cSCC who are not good candidates for surgery and/or chemotherapy.[50] This was based on the phase II study of EMPOWER-CSCC 1 trial, where they evaluated cemiplimab 3 mg/kg once every 2 weeks or 350 mg once every 3 weeks. The final analysis of the three groups studied showed an ORR of 50.8% (3 mg/kg) for metastatic cSCC, 44.9% (3 mg/kg) for locally advanced cSCC, and 46.4% (350 mg) metastatic cSCC.[51] OS at 48 months was 61.8%, with a median duration of response at 41.3 months, with fatigue as the most common treatment-emergent adverse event.[51] Although EMPOWER-CSCC was not specific for orbital and periorbital SCC, smaller studies with cemiplimab when used for orbit and ocular adnexa have shown promise.[52,53] Furthermore, small multi-institution study of cemiplimab showed a complete response of 82%, which authors suggest cemiplimab as a promising globe-sparing option for orbital SCC.[54,55]

Summary: Cemiplimab is a good option for patients with advanced cSCC, while pembrolizumab also shows promise. Cetuximab appears to be more effective as a neoadjuvant agent when paired with platinum or fluorouracil-based chemotherapy.

Periocular cutaneous melanoma

Primary eyelid (cutaneous) melanoma results from the malignant proliferation of melanocytes, more common in less pigmented races, and surgery is considered as the primary treatment. The BRAF signalling pathway is responsible for normal cell proliferation and survival in melanocytes. Unlike in uveal melanomas, about 50% of cutaneous melanomas have mutations in the BRAF gene.[56]

Targeted therapy in eyelid and periocular melanoma.

Vemurafenib. Vemurafenib was the first approved BRAF inhibitor for the treatment of Stage IIIC and IV metastatic melanoma. In a Phase I study, vemurafenib exhibited remarkable clinical activity as a single agent, inducing complete or partial tumor regression in 81% of patients and achieving a 56% response rate among those with the BRAF V600E mutation.[57] This was followed by Phase II studies where patients were given oral vemurafenib 960 mg twice daily. Confirmed ORR for the phase II study was 53%, with a median duration of response at 6.7 months and a median PFS at 6.8 months.[58] In addition, the Phase II study showed a median overall survival of 15.9 months, an unprecedented outcome for patients with advanced melanoma at that time.[59]

The promising results of phase I and II studies of vemurafenib prompted the BRIM-3 trial[60](Phase III), which compared vemurafenib to the reference chemotherapy drug dacarbazine. Median OS was significantly longer for the vemurafenib group (13.6 months vs. 9.7 months with dacarbazine), with significantly increased median PFS (6.9 months vs. 1.6 months for dacarbazine). A significant increase in ORR was also noted in the vemurafenib group at 57% compared to the dacarbazine group (9%).[60] Common adverse events of vemurafenib use in the BRIM-3 trial include arthralgia, rash, and fatigue.[60]

Dabrafenib. BREAK-3 was a phase III trial that evaluated the BRAF inhibitor dabrafenib vs. dacarbazine. Results showed a median PFS of 6.9 months for dabrafenib compared to 2.7 months for dacarbazine, as well as an ORR of 50% for dabrafenib vs. 6% for dacarbazine.[61] These results were comparable to BRIM-3 trial (vemurafenib), showing the superiority of BRAF targeted therapy vs. the current standard chemotherapy with dacarbazine. The most common adverse events with dabrafenib include hyperkeratosis, headache, arthralgia, and pyrexia.[61]

Dabrafenib+trametinib. While targeted therapy with a BRAF inhibitor can effectively produce tumor response and increase overall survival in melanoma patients, it is often accompanied by the development of resistance within a relatively short period of 5–7 months.[62] Studies combining a BRAF inhibitor with a MEK inhibitor, however, delayed the onset of resistance compared to monotherapy with BRAF inhibitor alone.[63]

To circumvent BRAF resistance, the COMBI-d trial evaluated the combination of 150 mg twice daily dabrafenib and 2 mg once daily trametinib (MEK inhibitor) vs. dabrafenib alone for stage IIC and IV melanoma.[64] ORR was 68% for combination with dabrafenib and trametinib vs. 55% for dabrafenib alone. Moreover, 3-year OS was higher for combination therapy (44% dabrafenib + trametinib vs. 32% dabrafenib alone), as well as for 3-year PFS (22% dabrafenib + trametinib vs 12% dabrafenib alone).[64]

Another trial, COMBI-v, evaluated the efficacy of dabrafenib combined with trametinib versus vemurafenib monotherapy. Results for the BRAF+MEK combination were more favorable, with the response rate for dabrafenib and trametinib at 64% vs. 51% for vemurafenib alone. Overall survival was also higher at 72% for combination vs. 65% for vemurafenib monotherapy.[65] Pooled results from both COMBI-d and COMBI-v trials showed that treatment with dabrafenib and trametinib showed an overall 5-year survival of 34%, while those patients with complete response had higher five-year survival at 71%.[66] When compared to monotherapy, the combination of dabrafenib and trametinib resulted in a higher occurrence of several adverse events, which included pyrexia, chills, and diarrhea. However, monotherapy resulted in a higher incidence of hyperkeratosis and alopecia.[64]

Vemurafenib+cobimetinib. CoBRIM was a Phase III trial that investigated the combination of vemurafenib with cobimetinib versus vemurafenib monotherapy with a placebo. The coBRIM trial found an increase in median PFS of 9.9 months for the combination group vs. 6.2 months in the monotherapy group, and a significantly higher ORR of 68% in the combination group vs. 45% in the monotherapy group. Median OS was also higher in the combination group at 22.3 months vs. 17.4 months for the monotherapy group.[67] Furthermore, in BRAF inhibitor naïve patients, the BRIM-7 trial showed that a combination of vemurafenib and cobimetinib shows a higher confirmed ORR of 87% and a median OS of 31.2 months.[68] The most common adverse events associated with the combination of vemurafenib and cobimetinib include rash, arthralgia, and diarrhea.[67]

Encorafenib+Binimetinib. The COLUMBUS trial investigated the BRAF inhibitor encorafenib with MEK inhibitor binimetinib vs. monotherapy with either encorafenib or vemurafenib alone for Stage IIIC-IV, unresectable, or metastatic cutaneous melanoma. The overall response for encorafenib and binimetinib combination was 63%, vs. 51% for encorafenib alone and 40% for vemurafenib alone. Additionally, encorafenib with binimetinib combination had a more favorable adverse event profile, resulting in fewer toxic effects and discontinuations.[69] When evaluated long term, OS was higher for encorafenib and binimetinib combination therapy at 33.6 months, vs. 23.5 months for encorafenib monotherapy and 16.9 months for vemurafenib monotherapy.[70] The most common adverse event associated with the combination of encorafenib and binimetinib includes nausea, diarrhea, and vomiting.[69]

Immunotherapy in eyelid and periocular melanoma.

Ipilimumab. Ipilimumab is a CTLA-4 monoclonal antibody approved by the FDA for the treatment of inoperable AJCC stage III and stage IV cutaneous melanoma. Phase III clinical trial with ipilimumab given as first line investigated the combination of ipilimumab (10 mg/kg) with standard-of-care dacarbazine (850 mg/sqm) compared to dacarbazine plus placebo for previously untreated metastatic melanoma. Results showed that OS was significantly longer for ipilimumab and dacarbazine combination (11.2 months) vs. dacarbazine and placebo (9.1 months). Survival rate was also higher for the combination group at one year (47.3% vs. 36.3%), two years (28.5% vs. 17.9%), and three years (20.8% vs. 12.2%).[71] Notable adverse events seen in this trial include diarrhea, pruritus, and rashes, and an increase in hepatic ALT and AST.[71] Rare reported ocular and periocular side effects of ipilimumab include anterior uveitis, facial nerve palsy, and giant cell arteritis.[39]

Pembrolizumab. Pembrolizumab was the first antagonist against the PD-1 receptor approved by FDA for metastatic melanoma. A landmark trial for pembrolizumab compared to ipilimumab was conducted to study its efficacy and safety in ipilimumab-naïve and ipilimumab-treated patients. ORR was significantly higher when pembrolizumab was given to ipilimumab-naïve (40%) compared to ipilimumab-treated (28%) patients.[72] KEYNOTE-002 was a phase II clinical trial that evaluated two doses of pembrolizumab vs. investigators' choice of chemotherapy (ICC) for advanced melanoma. The study showed that pembrolizumab had a higher overall response rate (21% for 2 mg, 25% for 10 mg, 4% for ICC) and higher 6-month PFS (34% for 2 mg, 38% for 10 mg, 16% for ICC).[74] KEYNOTE-006, on the other hand, was a randomized phase III trial comparing two dosing schedules of pembrolizumab vs. ipilimumab. ORR was 33% for pembrolizumab group and 12% for ipilimumab.[73] Moreover, a recent 5-year update on KEYNOTE-006 showed that in surviving patients, the median OS was 32.7 months in the combined pembrolizumab and ipilimumab groups.[74] Adverse events commonly seen with pembrolizumab use include fatigue and pruritus.[75] Meanwhile, rarely reported ocular and periocular side effects of pembrolizumab include anterior uveitis and Graves-like and myasthenia-like orbital disease.[39]

Nivolumab. Nivolumab is a fully human anti-PD-1 monoclonal antibody and is the second anti-PD-1 receptor approved by FDA. CheckMate 037 was a randomized phase III trial that investigated 3 mg/kg nivolumab compared to ICC. The overall response rate (27% vs. 10%) and median duration of response (32 vs. 13 months) were higher for nivolumab vs. ICC.[76] CheckMate 067, on the other hand, was a phase III double-blind study comparing nivolumab plus ipilimumab (NIVO+IPI) to nivolumab alone (NIVO) and to ipilimumab (IPI) alone in treatment-naïve patients with advanced melanoma. Results from CheckMate 067 showed that nivolumab groups had superior clinical activity vs. ipilimumab group, with higher overall response rate (57.6% NIVO+IPI, 43.7% NIVO, 19% IPI) and median PFS (11.5 NIVO+IPI, 6.9 NIVO, 2.9 IPI).[77] Adverse events commonly seen with nivolumab use include fatigue, pruritus, and diarrhea.[76] Rarely reported ocular and periocular side effects of nivolumab include anterior uveitis and Graves-like orbital disease.[39]

Summary: A combination of BRAF and MEK inhibitor is needed to circumvent resistance to targeted therapy, which shows good clinical outcomes and safety profile compared to standard chemotherapy. Immunotherapy with Ipilimumab, Pembrolizumab, and Nivolumab has also demonstrated good clinical outcomes and safety.

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare, highly aggressive neuroendocrine malignancy.[78,79] It is twice as lethal as melanoma,[78] with high mortality.[79,80] Five-year overall survival rate for MCC is 55.6% for localized disease, 35.4% for regional nodal disease, and a mere 13.5% for those with distant metastasis.[80] The lack of effective treatment options for MCC is reflected in the modest survival rates.[80] Until recently,[81] chemotherapy and/or radiotherapy have been the mainstay treatment approach for patients with advanced MCC.[82,83] Though initially chemosensitive, responses are usually not durable, as one study had an ORR of 55% but a median PFS of only 94 days.[84]

MCC is an immunogenic tumor, and infection with Merkel cell polyomavirus (MCPyV) has been detected in 80% of MCC cases.[85,86] To evade the immune response, MCC tumor cells express programmed cell death ligand–1(PD-L1), which signals to PD-1 on activated anti-tumor T-cells and causes their inactivation.[33] This immune checkpoint is commonly exploited by immunogenic tumors like MCC to promote immune quiescence. Targeting this immune checkpoint by antibodies that bind to either PD-L1 or PD-1 has been proven effective in re-activating immune anti-tumor response that results in tumor regression.[87]

Immunotherapy in Merkel cell carcinoma.

Avelumab. Avelumab is a PD-L1 monoclonal antibody approved by the FDA for the treatment of MCC, based upon the success of the JAVELIN Merkel 200 trial.[88] The trial consisted of two parts. Part A evaluated patients who progressed despite chemotherapy.[89] Part B studied avelumab as the first-line treatment for MCC.[90] Five-year long-term follow-up for patients under Part A of Javelin Merkel 200 showed an ORR of 33% and median OS of 12.6 months, with overall survival rates of 32%, 30%, and 26% at 3, 4, and 5 years, respectively.[89,91] This result is a stark contrast to the usual chemotherapy regimen, which only has an ORR of 8% and a 6- and 12-month overall survival rate of 27.5% and 0%, respectively.[92] Part B of JAVELIN Merkel 200 trial was a separate parallel cohort that evaluated avelumab for chemotherapy naïve patients with advanced MCC. It showed an ORR of 39.7% and a median OS of 20.3 months.[90] These results indicate that Avelumab is superior to classic chemotherapy regimens for advanced MCC.[84,93] Adverse events commonly associated with nivolumab use include fatigue and infusion-related reactions (fever and chills).[88]

Pembrolizumab. KEYNOTE-017 was a phase II trial that investigated pembrolizumab as a first-line agent for MCC.[94] At a 3-year follow-up since the start of the trial, pembrolizumab showed an ORR of 58%, with a median OS of 59.4% for all patients. Moreover, for those who were responders to pembrolizumab, the median OS was higher at 89.5%.[93,95] Objective regression was also observed in both Merkel cell polyoma virus-positive and negative tumors.[95] These results demonstrated better tumor control and better overall survival compared with historical data from patients treated with chemotherapy.[84,93]

Nivolumab. Nivolumab was also evaluated for advanced MCC with phase I/II multiple cohort CheckMate 358 study. Though the study only had 25 patients, nivolumab demonstrated an ORR of 64%.[96] When nivolumab was given as a neoadjuvant 4 weeks before surgery, there was substantial (>30%) radiologic tumor regression in 45% of patients and pathologic tumor regression in 65% of patients. Moreover, most patients who underwent surgery remained tumor-free at 12 months.[97]

Summary: Immunotherapy for MCC with avelumab, pembrolizumab, and nivolumab shows better outcomes and safety profile than the standard chemotherapy.

Sebaceous gland carcinoma

Sebaceous gland carcinoma (SGC) is a malignant tumor of the sebaceous glands, more commonly found in the periorbital region and in patients of Asian ethnicity.[98]

The current standard of care for SGC involves wide surgical resection or chemotherapy with anthracycline or platinum-based regimens for those with metastasis.[98] To date, no targeted or immunotherapy drugs have been approved for use in SGC. However, there are isolated case reports of anti-PD-1 immunotherapy drug pembrolizumab usage with promising results.[99,100] Other potential recommended targets currently explored for metastatic SGC include anti-androgen, retinoid receptor ligands, and EGFR inhibitors.[101]

Summary: While there is currently no targeted/immunotherapy approved for SGC, pembrolizumab shows promise.

Orbital tumors

Common orbital tumors may be classified into benign, premalignant, and malignant lesions. Most benign tumors are well circumscribed and may either be observed or surgically excised, confirmed histopathologically, and when indicated immunohistochemically. Occasionally some of these may be either recurrent or become aggressive and turn malignant from residual lesions, especially when incompletely excised.[102]

Solitary fibrous tumor

Solitary fibrous tumor (SFT) is a rare soft tissue tumor of mesenchymal origin. When incompletely excised, they have the potential for malignant transformation and even distant metastasis. Historically, targeted therapy with antiangiogenics has been evaluated with a modest response.[103–105] Pazopanib is a small-molecule tyrosine kinase inhibitor that acts via inhibition of the intracellular tyrosine kinase of VEGF and PDGF receptors.[106] A Phase II trial of Pazopanib for the treatment of advanced malignant and dedifferentiated SFT evaluated 40 patients with a median follow-up of 27 months, showing 51% of the patients had partial responses, 26% had stable disease, and 23% had progressive disease.[107] Similarly, a phase II study using the tyrosine kinase inhibitor axitinib was also evaluated against SFT.[108] Despite this, there are currently no approved targeted or immunotherapy drugs for SFT.

Summary: There is currently no targeted/immunotherapy approved for SFT, although pazopanib and axitinib show promise.

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma Protuberans (DFSP) is the most common dermal sarcoma.[109] It has a 25% risk of local recurrence at 5 years[110] but a low 2–5% risk of metastasis.[111] Complete surgical resection with negative margins is the mainstay management, as inadequate initial resection may result in local recurrence or disease progression.[110,112] The discovery of genetic translocation involving chromosomes 17 and 22 in more than 90% of DFSP led to the identification of platelet-derived growth factor subunit β (PDGFβ) as a potential target.[113]

Targeted therapy for Dermatofibrosarcoma Protuberans.

Imatinib. Imatinib is a tyrosine kinase inhibitor (TKI) with activity against several tyrosine kinase enzymes.[114] Imatinib was approved by the FDA after a Phase II study demonstrating its efficacy for DFSP, with ORR approaching 50% and a 1-year OS rate of 87.5%.[115] Most studies with imatinib, however, were designed as neoadjuvant to surgery, where imatinib was started to make the tumor amendable for surgery.[115–117] In a systemic review of studies done for imatinib, pooled data showed complete or partial response rates of 60.5%, a stable disease rate of 27.6%, with 88.1% of patients with DFSP showing some degree of clinical benefit to imatinib.[118] Leukopenia is the most commonly seen adverse event with imatinib use.[115]

Summary: Imatinib has shown clinical benefits against DFSP.

Meningioma

Meningiomas are relatively common intracranial and less common intraorbital tumors. Intraorbital meningiomas include optic nerve sheath meningiomas and sphenoid wing meningiomas. Intracranial meningiomas are the most common primary brain tumor in adults, and they sometimes extend to the orbit.[119] Despite being generally benign and histopathologically of low grade, these meningiomas may exhibit relentless progression that is unresponsive to radiotherapy or debulking and can be locally aggressive.[120] Historically, the 6-month PFS rate for untreated recurrent meningioma is only 11–15%.[121] Studies with meningioma found a strong constant expression of Somatostatin Receptor 2A (SSRT2A) and activation of the mammalian target of the rapamycin (mTor) pathway.[122] Other pathways being considered include targeting the VEGF pathway with bevacizumab and apatinib, which also show promise in small case series studies.[123,124]

Targeted therapy for meningiomas.

Everolimus+octreotide. Somatostatin receptor 2 (SSTR2) expression is well established in meningiomas, and it is specifically targeted by octreotide, a somatostatin analog. Considering the role of the mTOR pathway and the expression of SSTR2A receptors in meningiomas, a recent study has shown that the

combination of octreotide and everolimus, an mTOR inhibitor, produces an additive effect. CEVOREM is a phase II trial that evaluated the combination of everolimus and octreotide for recurrent meningiomas. Results from CEVOREM trial showed a 6-month PFS of 55%,[120] which is much higher than the historical data (only 11–15%).[121] Furthermore, OS rates for 6 and 12 months are 90% and 75%, respectively, with a significant decrease (>50%) in growth rate observed in 78% of tumors at 3 months.[120] Adverse events commonly seen in CEVOREM trial include stomatitis, fatigue, abdominal pain, and hypercholesterolemia.[120]

Sunitinib. Sunitinib is a tyrosine kinase inhibitor that inhibits multiple signaling pathway, which includes VEGF receptor, PDGF receptor, and KIT.[125] A phase II trial was done for sunitinib in patients with recurrent WHO grade II-III with an endpoint of 6 months PFS. The study met the primary endpoint with a 6-month PFS of 42% and a median OS of 24.6 months.[126] Recently, sunitinib was compared with octreotide + everolimus, where it showed a PFS of 9.1 months vs. 12.1 months from octreotide + everolimus.[127]

Summary: The combination of everolimus and octreotide and sunitinib shows promise for meningioma, though further studies must be done.

Neurofibromatosis

Neurofibromatosis Type-I (NF1) is a common autosomal dominant disorder affecting 1 in 3000 at birth.[128] NF1 is caused by mutations to the NF1 gene, resulting in the loss of its protein product, neurofibromin. Neurofibromin is a negative regulator of RAS signaling, and loss of this results in activation of the RAS-MAPK signaling cascade, resulting in cell proliferation and tumor formation.[129] MEK1 and MEK2 are kinases found in the RAS-MAPK pathway, and inhibition of both MEK signaling inhibits the RAS-MAPK pathway, famously seen in melanoma. [63]

Targeted therapy for neurofibromatosis.

Selumetinib. Selumetinib is a highly selective, ATP-uncompetitive allosteric inhibitor of both MEK1 and MEK2, thereby inhibiting the expression of the RAS-MAPK pathway.[130] It is the first FDA-approved drug for the treatment of pediatric NF1 patients aged two and above who have symptomatic and inoperable plexiform neurofibromas. This is based on the results of Phase II of the SPRINT trial, which demonstrated a 27.7% reduction in the volume of plexiform neurofibromas, a best partial response of 72%, and stable disease in 24%.[131] These responses were durable, lasting more than a year.[131] The most frequent side effects of selumetinib use include gastrointestinal symptoms, asymptomatic creatine kinase increase, and acneiform rash.[131]

Summary: Selumetinib, a MEK inhibitor, shows promise for neurofibromatosis, though further studies need to be done.

Langerhans cell histiocytosis

Langerhans Cell Histiocytosis (LCH) is a myeloproliferative disorder that features inflammatory lesions with abundant CD1a+/CD207+ histiocytes that lead to the destruction of the affected tissue.[132] The discovery of BRAF-V600E mutations in 57% and the activation of the MAPK pathway in patients with LCH led to the interest in using BRAF inhibitors.[133] Though there are no currently approved targeted therapy drugs for LCH, BRAF inhibitors such as vemurafenib and dabrafenib are among those that show promise. In a recent study of 54 pediatric patients with refractory multisystem LCH, 38 patients had complete responses, while 16 had a partial response with vemurafenib (20 mg/kg/day) at 8 weeks. However, when discontinued, reactivation was seen in 80%.[134] Dabrafenib was also recently studied in 20 pediatric patients with BRAFV600E mutated LCH, with an ORR of 65%.[135]

Summary: BRAF inhibitors such as vemurafenib and dabrafenib show promise for LCH, though further studies need to be done.

Ocular adnexal lymphoma

Ocular adnexal lymphoma (OAL) is the most frequent type of malignant orbital tumor in adults.[136] Most of these tumors are low-grade B-cell non-Hodgkin's lymphoma (NHL) that arise from either precursor cells or mature lymphocytes. B-cells are the most commonly affected type (80%), followed by T-cells (14%) and, rarely, Natural Killer (NK) cells (6%).[137] Although lymphomas of various subtypes can develop in the orbit, the most prevalent histologic types of ocular adnexal lymphoma are extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), follicular cell lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma which most of them commonly originate from B-cells.[138] Treatment for ocular adnexal lymphoma varies based on presentation, histologic subtype, and systemic involvement, with the mainstay options being orbital radiotherapy and systemic chemotherapy.[139] The identification of CD20, a transmembrane protein that is found on mature B-cells and most B-NHL cells, has made it a site for immunotherapy.[140] Unlike pro-B cells and antibody-producing plasma cells, it does not express CD20, so anti-CD20 treatment does not affect healthy B-cells.[141]

Other therapeutic targets being investigated for treating relapsed and refractory lymphomas include the Phosphatidylinositol 3-kinase (PI3K) pathway, which can be targeted with drugs like idelalisib, copanlisib, and duvelisib.[142] While their use has not yet been established for OAL, these agents show promise.

Immunotherapy in ocular adnexal lymphoma.

Rituximab. Rituximab was the first immunotherapy drug approved by FDA for treating patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma more than 25 years ago.[142] By binding to the CD20 surface antigen, which is present in 90% of malignant B-cells, rituximab can block the downstream complement-mediated pathways that would otherwise lead to cell proliferation.[143]

The IELSG-19 phase III study aimed to evaluate the effectiveness of adding rituximab to chlorambucil in improving event-free survival (EFS) for patients with extranodal marginal zone B-cell lymphoma of MALT and examined the use of the current choice of chemotherapy monotherapy agent chlorambucil vs. rituximab monotherapy and vs. combination therapy of chlorambucil and rituximab. The final result of the IELSG-19 study showed that after a median follow-up of 7.4 years, the addition of rituximab to chlorambucil significantly improved EFS. The EFS at 5 years was found to be 51% with chlorambucil alone, 50% with rituximab alone, and 68% with the combination.[144] The combination arm also showed a significant improvement in progression-free survival.[144]

Moreover, in the phase III trial AUGMENT, the combination of lenalidomide plus rituximab versus placebo plus rituximab was conducted in patients with relapsed and/or refractory follicular or marginal zone lymphoma. The median PFS assessed by the independent review committee was 39.4 months with lenalidomide plus rituximab versus 14.1 months with placebo plus rituximab. The ORR also, when assessed by the independent review committee, was better with lenalidomide plus rituximab at 78%, vs. only 53% for rituximab with placebo.[145]

Intralesional rituximab for CD20+ OAL has also shown to have promising results.[146–148] Known adverse events for systemic rituximab include neutropenia, diarrhea, constipation, fatigue, and fever, while for intralesional rituximab include pain at the injection site and fever.[149,151,152]

Targeted therapy for ocular adnexal lymphoma.

Ibrutinib. Ibrutinib is a potent inhibitor of Bruton tyrosine kinase (BTK), which plays a crucial role in the B-cell receptor signaling pathway. It has been approved by FDA for the treatment of relapsed or refractory mantle cell lymphoma (MCL).[149] This approval was based on the results of a single-arm phase II multicenter trial, which investigated the use of 560 mg ibrutinib in a patient with relapsed or refractory MCL. ORR was 68%, where 21% had a complete response, while 47% had a partial response. The overall survival rate was 58% in 18 months.[149] These findings were mirrored in a similar study where ibrutinib was used as a second-line drug as well, with an ORR of 69% and a median OS of 23.9 months.[150] The most common adverse events include diarrhea, fatigue, and nausea.[149]

Summary: Immunotherapy with rituximab has shown to be effective, particularly when combined with chlorambucil or lenalidomide. Intralesional rituximab and targeted therapy on PI3K pathway also show promise. Ibrutinib, on the other hand, is a good option for refractory cases of MCL.

Orbital lymphatic malformation

Previously called orbital lymphangiomas, orbital lymphatic malformations (ISSVA classification) are tumor-like congenital malformations that are fluid-filled due to abnormal lymphatic development.[151] Although they can present anywhere in the body, approximately 20% occur in the orbit and surrounding adnexa.[152–154] Currently, no large randomized clinical trial exists for orbital lymphatic malformation. Potential targets, however, include the mTOR pathway inhibition, for which sirolimus is currently being used in some small series.[155,156] Recently, in a systemic review that pooled ten patients who underwent sirolimus treatment for orbital lymphatic malformation, seven patients (70%) had partial response, while three patients (30%) had a complete response. It has been noted that no patients had an absent response, while the time to response ranged from 2 weeks to 7 months.[155] Adverse effects noted with sirolimus include mild reversible leukopenia and mild hypertriglyceridemia.[155,156]

Summary: The use of sirolimus for orbital lymphatic malformation shows promise, although more studies need to be done.

Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) is the most common malignant tumor of the minor salivary gland, and in rare instances may occur in the lacrimal gland and nasolacrimal duct.[157] Lenvatinib, a tyrosine kinase inhibitor, was recently investigated in a phase II trial for recurrent or metastatic ACC of salivary origin.[158] In this trial, only partial response was observed at 15.6%, while 75% had stable disease. However, more than half (56%) of the patients

discontinued lenvatinib due to drug-related issues, with the most common adverse events, including hypertension and oral pain.[158] These results were closely reflected in another trial, in which patients with lenvatinib only had partial responses (11.5%) with a high rate of treatment-related adverse events (96%).[159] Lenvatinib was also evaluated as monotherapy, but objective radiological responses by RECIST were not observed in any patient in this study.[160] Of note, however, that tumor reduction with lenvatinib was seen in 66% of patients, with 25% showing a 20% or greater reduction in tumor size.[159]

Summary: Lenvatinib shows promise in early trials but is associated with high rate of treatment-related adverse events and discontinuation rate.

Summary

The advent of targeted and immunotherapy has offered a paradigm shift to the management of advanced and metastatic cancers. With both targeted and immunotherapy, cancer was no longer fought on a cellular level as most traditional chemotherapy, but rather on a molecular level, which is rapidly and ever-expanding. With our ever-increasing understanding of the molecular and immune pathways of cancers, more agents and neoplasms, not just of the periocular and periorbital region by the head and neck and systemically as well, are now being investigated. This reflects the emerging shift of management of benign and malignant neoplasms from a conventional "one-size-fits-all" or "shotgun" approach to somewhat customized or personalized management, with minimal toxicity while improving survival and quality of life. Costs and availability, however, are still limitations for both targeted and immunotherapy at the present, which eventually will be overcome with widespread adoption and evidence. We, therefore, conclude that while neoadjuvant chemotherapy and palliative chemotherapy with or without radiation still play a role today, targeted and immunotherapy are poised to become a significant therapeutic tool in the management of advanced and otherwise unresectable periocular and periorbital neoplasms either alone or in combination with other modalities.

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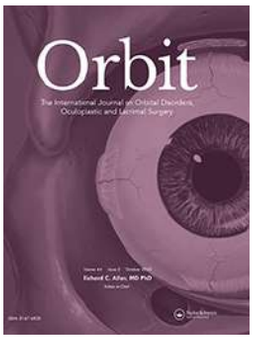

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Orbital and ocular adnexal histiocytic tumors; a multidisciplinary literature review

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REVIEW ARTICLE

Orbital and ocular adnexal histiocytic tumors; a multidisciplinary literature review

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ABSTRACT

Purpose: To review and update the clinical presentation, pathology, treatment strategies, and follow-up of the orbital and ocular adnexal histiocytic tumors.

Methods: The review included the publications in English literature up to January 2024.

Results: Out of 263 screened publications, 73 studies on Langerhans cell histiocytosis (LCH), juvenile and adult onset xanthogranuloma (JXG, AOXG), Erdheim-Chester disease (ECD), Rosai-Dorfman disease (RDD), and histiocytic sarcoma (HS) were included. Diagnosis is based on histological characteristics and markers on immunohistochemical staining. Treatment options vary depending on the type of histiocytic tumors, number of lesions, number of involved organs, and presence of vital organ involvement such as central nervous system. Surgery is the first diagnostic step for all and serves as the primary treatment for LCH and XG. Systemic chemotherapy is the primary treatment for EDC, RDD, and HS and the treatment of choice for the patients with multifocal or multi-organ involvement as well as recurrent or refractory lesions, regardless of the type of histiocytic tumor. Radiotherapy is an adjunctive primary treatment for the patients with HS. It is reserved for recurrent or refractory lesions in the other types. Targeted therapy is currently in progress and may replace the systemic chemotherapy in patients with LCH, XG, and EDC.

Conclusion: Surgical debulking is diagnostic in all and therapeutic in LCH, JXG, and AOXG. All recurrent, refractory, multifocal, and multi-organ tumors require additional systemic chemotherapy with or without radiotherapy. Follow-up imaging every 3 to 6 months for the first 2 years and then annually is recommended.

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Introduction

Histiocytosis is a diverse group of disorders characterized by the accumulation of cells derived from dendritic cells or macrophage precursors.[1] Orbital histiocytic tumors represent only a small fraction of the orbital tumors.[2,3] Recent advances in the molecular genetics of histiocytosis and histiocytic neoplasms suggest a common genetic foundation across the various forms.[4–6] There are diverse modalities for treating orbital and ocular adnexal histiocytic tumors including surgery, radiation, chemotherapy, and immunotherapy. Since this review focuses on the subtypes with documented orbital and ocular adnexal involvement, it will review the updates on 5 groups of the histiocytosis with orbital and ocular adnexal involvement including Langerhans cell histiocytosis (LCH), juvenile and adult onset xanthogranuloma (JXG, AOXG), Erdheim-Chester disease (ECD), Rosai-Dorfman disease (RDD), and histiocytic sarcoma (HS) or malignant histiocytic disorders.

Method of literature review

The search strategy was conducted across several databases including PubMed, Google Scholar, and Cochrane Library. It contained all the peer-reviewed publications in English language up to January 2024. The keywords used in combination were "histiocytosis," "orbit," "classification," "clinical characteristics," "pathology," "radiation," "surgery," "chemotherapy," and "target therapy." The process of literature searches and selecting the articles

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were performed by a review team from oculofacial plastic surgery, pathology, radiotherapy, and medical oncology departments.

Results

Out of 263 screened publications, 73 were included in the review. The first proposed classification of histiocytic disorders (1987) was based on cellular origins, molecular pathology, and clinical features which consisted of LCH, histiocytoses of mononuclear phagocytes other than Langerhans cells, and hemophagocytic lymphohistiocytosis or Malignant Histiocytosis.[7] This review, however, recruited the most recent classification of the histiocytic disorders with orbital and ocular adnexal involvement which includes LCH, JXG, AOXG, ECD, RDD, and HS.[8]

Epidemiology and clinical presentation (Supplementary Table 1)

LCH is most commonly diagnosed in early childhood with a median age of 3.8 years. Its incidence is estimated at 5–9 cases per million in individuals under 15 years. While males are more frequently affected, females have an earlier onset with a more aggressive disease course.[9] It's typical orbital presentation is a unilateral unifocal isolated osteolytic lesion with an associated soft tissue mass that infiltrates the superolateral orbital rim and roof.[10] The typical location is because of the natural migration of active hematopoietic bone marrow laterally as the frontal sinus develops (Figure 1(A)). In adults, the lesion more commonly affects the greater wing of the sphenoid (Figure 1(C)).[11] Based on the site and extent of orbital involvement, patients present with proptosis, eyelid mass, blepharoptosis, and or eyelid swelling. If the soft tissue component extends into the orbit, patients may experience diplopia, cranial nerve palsies, and optic disc edema.[12] Multifocality, multiple system involvement or bilateral sequential orbital involvement are rare.[12,13] Other uncommon ophthalmic manifestations of LCH could be ocular surface infiltrates, uveitis, choroidal infiltrates, posterior scleritis, and glaucoma.[10,11]

JXG (Figure 2(A,B)) is the most common non-LCH. It is considered a benign cutaneous and mucocutaneous histiocytic disorder mostly arising in early childhood with 5–12 months' median age of onset and predominantly affecting males.[14,15] Orange skin nodules in the head and neck region usually appear during the first year of life. Ocular (iris and choroid, optic nerve, and conjunctiva), eyelid, and orbital lesions are the most common extra-cutaneous sites occurring in 0.3 to 10% of children with cutaneous lesions.[15,16] *AOXG* (Figure 3(A,B)), on the other hand, is less common than JXG, occurs in adults with median age of 44.3 years, and frequently presents as a single or multiple subcutaneous lesion. Almost half of the patients develop elevated, yellowish nodules eyelid lesions resembling xanthelasma.[16]

ECD is a rare form of non-Langerhans cell histiocytosis that primarily affects men between 50s and 70s. Skeletal involvement occurs in 74% of the patients characterized by bilateral cortical sclerosis in the metaphysis and/or diaphysis of the lower extremity long bones.[17] Diabetes insipidus and proptosis are the most common non-bone manifestations.[17] Proptosis is present in 25% of the cases with bilateral multi-compartments including lacrimal gland involvement (Figure 4(A,B)).[13] Osteosclerosis of the skull and facial bones may also be present.[12] ECD can present as a retrobulbar pseudotumor, sometimes mimicking orbital inflammatory disorders with chorioretinal folds and disc swelling.[18,19] Eyelids or periorbital skin xanthelasma have also been reported in 18 – 28% of the patients.[20] When intraconal lesions compress the optic nerve, patients may develop optic disc edema and subsequent atrophy.[21]

RDD also known as sinus histiocytosis with massive lymphadenopathy is a rare nonmalignant histiocytic proliferation that primarily affects the head and neck.[22] RDD tends to occur in younger predominantly male individuals at a mean age of 20.6 years. The hallmark of RDD is painless cervical lymphadenopathy in over 80% of the cases.[22] Extranodal involvement occurs in 43% of cases with orbital and ocular adnexal manifestations in approximately 10% of the cases. However, isolated orbital and ocular adnexal involvement is rare.[23] A chronic painless proptosis resembling idiopathic orbital inflammation or lymphoproliferative disorders is the most common manifestation of the orbital involvement (Figure 5(A,B)). Other reported ophthalmic manifestations are epibulbar mass, compressive optic neuropathy, uveitis, scleritis, serous retinal detachments, corneal lesions, lacrimal duct obstruction, and choroidal mass.[23] Patients with ocular involvement often have more aggressive disease.[24]

HS is a rare aggressive histiocytic neoplasm which, despite its name, is not a true sarcoma. The most frequently involved organs are skin and connective tissues (41%a), lymph nodes (14%), gastrointestinal tract (12%), and hematopoietic system (9%).[25] Although it is rare in the head and neck region, HS has been reported in the orbit with extensive bone destruction and extension into adjacent sinuses.[26]

Histopathology (Table 1)

LCH presents with large (10–25 μm) histiocytes that are round to oval, frequently exhibiting nuclear contours

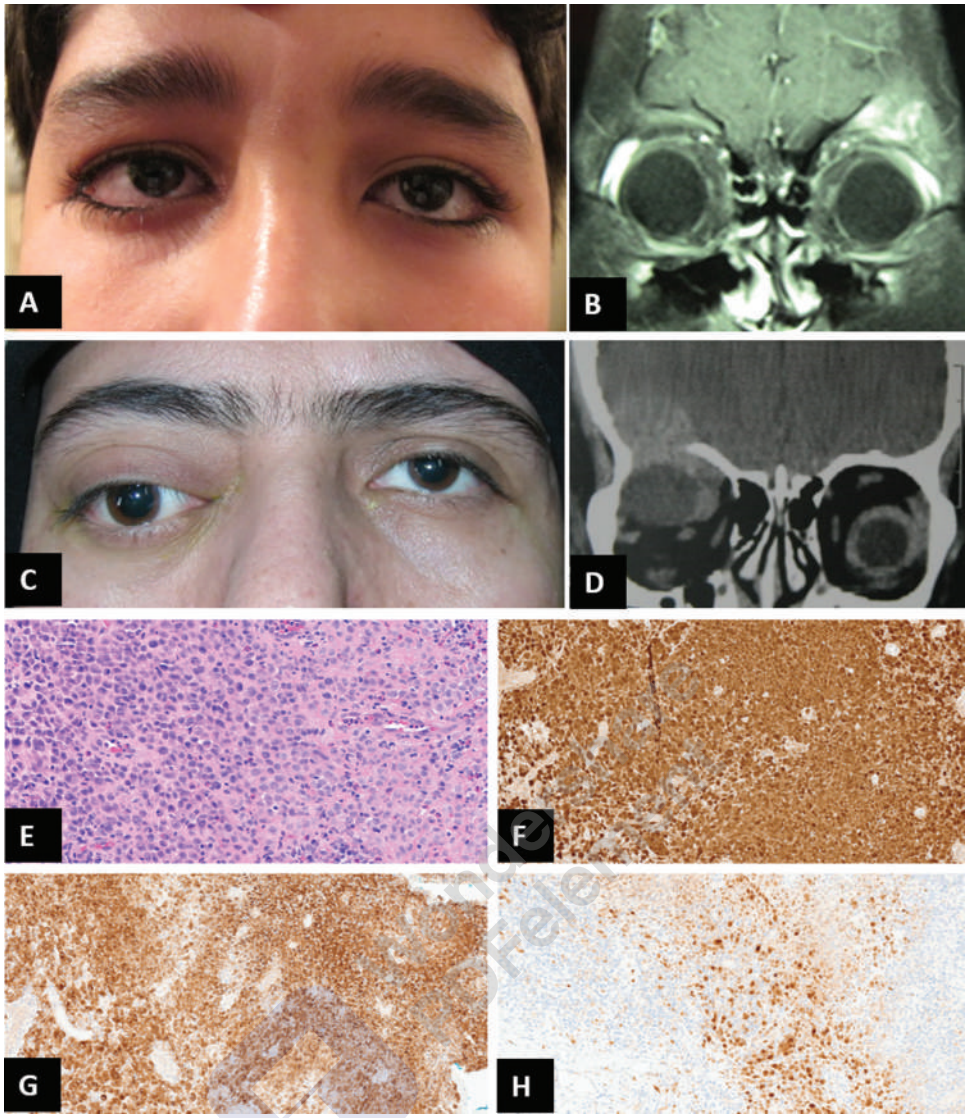

Figure 1. An 11-year male (A) with left Langerhans cell histiocytosis (LCH) whose T1 weighted magnetic resonance imaging (B) shows an enhanced bone lytic lesion at the superior and lateral of the left orbit. A 34-year female (C) with right LCH whose computed tomography scan (D) shows a bone lytic lesion with intracranial extension. Hematoxylin and eosin staining (E) shows multiple Langerhans cells with the typical nuclear contours/nuclear grooves, and an inflammatory infiltrate with eosinophils, lymphocytes, and plasma cells in the background. S100 immunohistochemical stain (F) is showing nuclear and cytoplasmic staining. There is positive granular cytoplasmic staining (G) in CD207 (langerin, birbeck granules surrogate). Positive b D1 (H) shows an overexpression of the Langerhans cell staining.

that assume a nuclear groove and moderately abundant eosinophilic cytoplasm (Figure 1(E)). The surrounding inflammatory infiltrate primarily consists of eosinophils and lymphocytes with plasma cells being less prominent. Mitotic activity or nuclear pleomorphism is not observed. As the disease progresses, Langerhans cells and inflammatory infiltrate are gradually replaced by fibrosis, making the diagnosis more challenging.[27]

Both cutaneous and extracutaneous *JXG* show one or more of three primary cellular types: mononuclear cells, multinucleated cells with or without Touton features, and spindle cells in varying proportions (Figure 2(C,D)).[28] The histopathological appearance of JXG correlates with the duration of inflammation.[29] In newly formed lesions, histiocytes are mixed with lymphocytes, plasma cells, neutrophils, and occasionally eosinophils. In mature lesions, histiocytes are usually foamy with characteristic Touton giant cells (exhibiting a ring of nuclei surrounded by foamy cytoplasm) which are observed in 85% of cases (Figure 2(D)).[7,30] Touton giant cells are less common in orbital and ocular adnexal JXG than cutaneous lesions. Fibroblasts and fibrosis are prominent features in the late-stage.[31] Histopathologic features of *AOXG* are marked by sheets of mononucleated foamy histiocytes

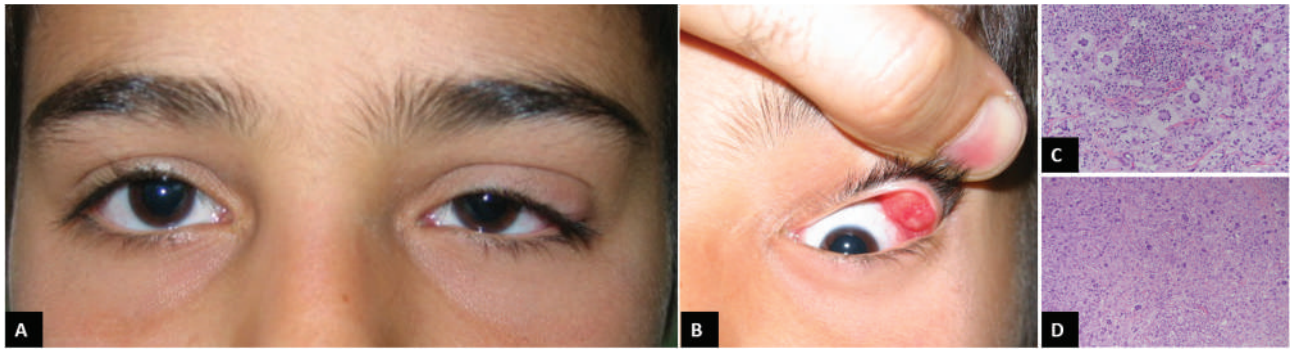

Figure 2. A 7-year-old male (A) with juvenile xanthogranuloma (JXG) involving the left upper eyelid (B). Hematoxylin and eosin staining (C) shows a mature-type JXG with the three primary cellular types: mononuclear cells, spindle cells, and multinucleated cells with and without Touton features. Closer view of Touton giant cells (D) exhibiting a ring of nuclei surrounded by foamy cytoplasm.

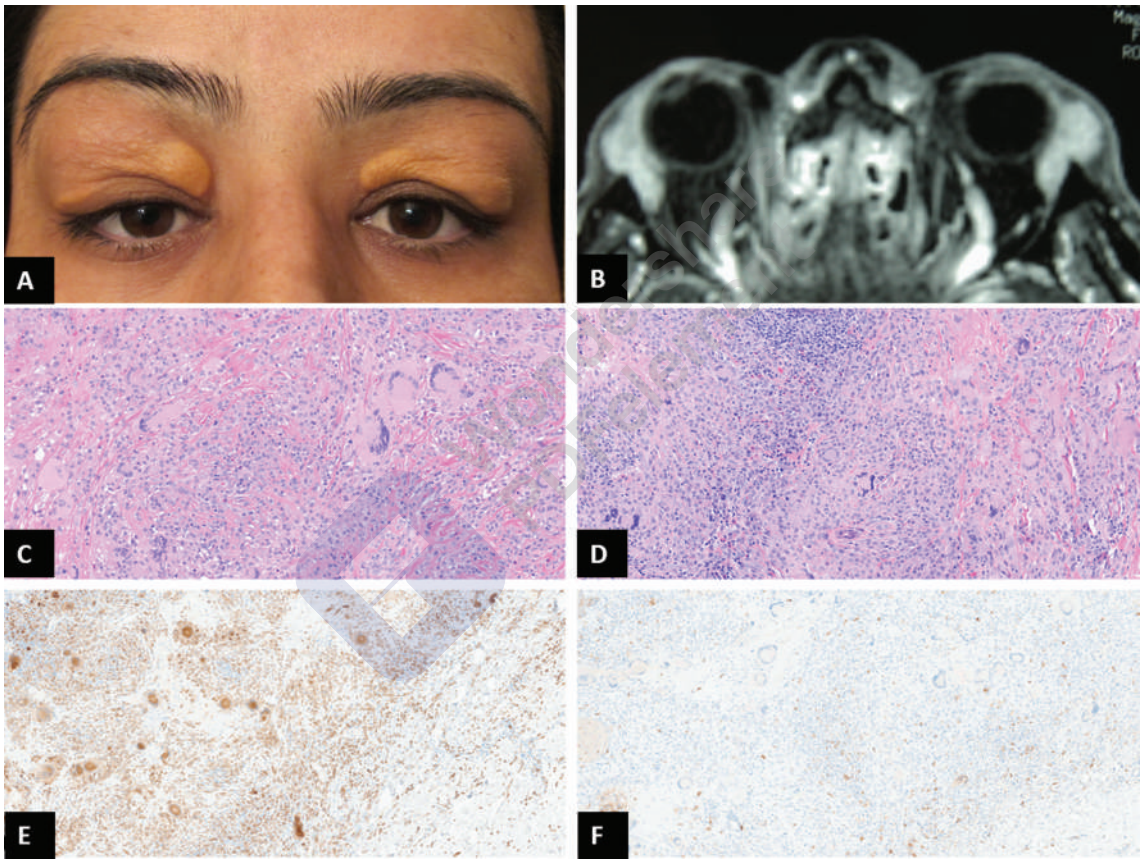

Figure 3. A 37-year-old female with adult onset xanthogranuloma (AOXG) involving the skin (A) lacrimal gland, and lateral orbit (B), bilaterally. Hematoxylin and eosin staining (C and D) shows sheets of mononucleated foamy histiocytes (xanthoma cells), accompanied Touton giant cells. The xanthoma cells of this case have small, round nuclei and clear cytoplasm; lymphoid aggregates, lymphocytes and eosinophils are present in the background. Positive CD68 (E) and negative S100 (F) in immunohistochemistry staining.

(Xanthoma cells) infiltrating the orbicularis muscles and orbital tissue, accompanied by varying numbers of dispersed or clustered lymphocytes, plasma cells, and Touton giant cells (Figure 3(C,D)).[32,33] Lymphoid follicles are frequently scattered throughout with varying reactive germinal centers. Fibrosis is often present to varying degrees and orbital fat necrosis is frequently present.[34]

In the *ECD*, histiocytic infiltrate commonly shows nodular to diffuse sheets of lipid-laden or eosinophilic histiocytes with classical xanthomatous features (Figure 4(C)). The reactive background stroma shows

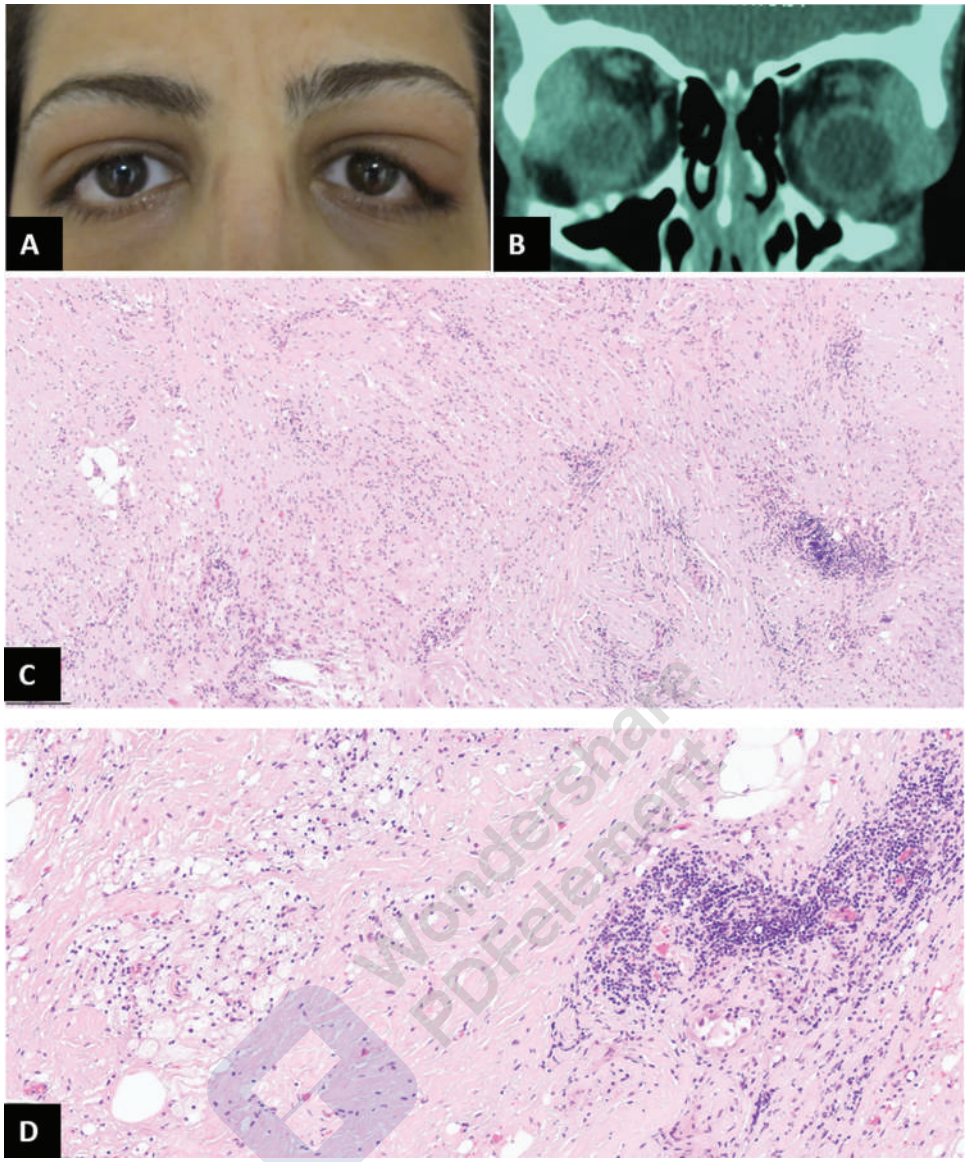

Figure 4. A 35-year-old female with Erdheim-Chester disease involving bilateral lacrimal glands on the clinical examination (A) and computed tomography scan (B). Hematoxylin and eosin staining (C) shows abundant fibrosis depicted in a background with scattered lymphocytes and lymphoid aggregates and a nodular sheet of lipid-laden histiocytes with classical xanthomatous features and lymphoid aggregates without germinal centers (D). No Touton-type giant cells were present, which made the diagnosis challenging.

nodular lymphoplasmacytic aggregates without germinal center formation with moderate to marked fibrosis (Figure 4(D)).[21]

RDD is characterized by an infiltrate of macrophages with central large ovoid prominent nucleoli and voluminous eosinophilic cytoplasm (Figure 5(D)). Classically, many RDD cells show lymphophagocytosis or emperipolesis with no xanthomatous features. Touton giant cells are usually absent. Fibrous septa separating the inflammatory infiltrates are commonly seen. A characteristic delicate branching pattern of capillaries cuffed by plasma cells and emperipolesis could also be present.[35]

HS is characterized by confluent sheets of discohesive, markedly atypical, and mitotically active cells. The neoplastic cells are large and polygonal, displaying epithelioid to pleomorphic morphology, copious eosinophilic to vacuolated or xanthomatous cytoplasm, ovoid to irregularly contoured nuclei, and variably prominent nucleoli (Figure 6(A)). They exhibit histiocytic differentiation with sporadic foamy histiocytes. Spindle cell morphology may be observed in a subset of cases. Tumor necrosis is conspicuous and a mixed inflammatory infiltrate is often extensive. Erythrophagocytosis may be present but is frequently subtle and obscured by the prominent inflammation.[36]

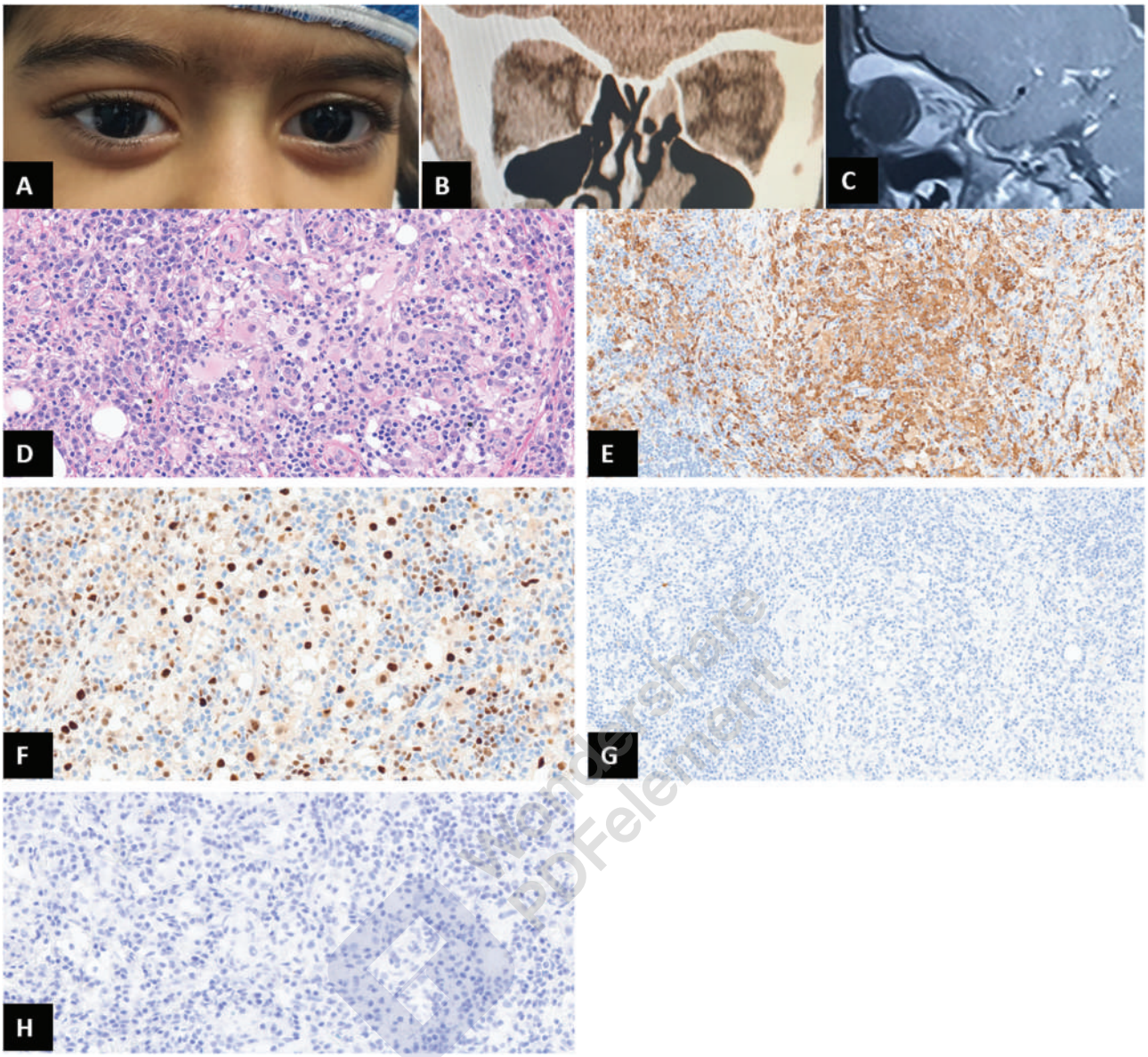

Figure 5. A 10-year-old male (A) with Rosai-Dorfman disease (RDD) involving the right superior rectus-levator complex at the superior orbit and inferior orbit (inferior rectus) on coronal orbital computed tomography scan (B) with enhancement on sagittal T1 magnetic resonance imaging (C). Hematoxylin and eosin staining (D) shows RDD macrophages with ovoid and large nuclei and voluminous eosinophilic cytoplasm, and in the center of the picture, emperipolesis with intact intracytoplasmic plasma cells. Plasma cells are also present in the stroma background. Immunohistochemical stains further support the diagnosis of RDD by positive CD68 (E) and OCT-2 (F) as well as negative CD1a (G) and CD30 (H).

Immunohistochemistry (Table 2)

Immunohistochemical markers help differentiate these conditions based on their cellular origin and protein expression. The *LCH* cells are typically positive for S100 (nuclear and cytoplasmic) (Figure 1(F)), CD207 (langerin granular cytoplasmic) (Figure 1(G)), CD1a (membranous or perinuclear) (Figure 1(H)), and CD68 (Golgi dot-like staining). Factor XIIIa and CD163 are usually negative. CD207 (Figure 1(G)) immunohistochemical stain is the surrogate for Birbeck granules which are tennis racket shaped organelles seen on ultrastructural examination of Langerhans cells.[37] The Ki-67 proliferation index is variable (typically <10% by double staining). Downstream markers of mitogen-activated protein kinase (MAPK) activation include nuclear cyclin D1 are usually positive and cytoplasmic phosphorylated ERK are variably positive.[38] VE1 antibody specific for mutant BRAF protein is positive in 50–60% and could be used in conjunction with nucleic acid-based assays to

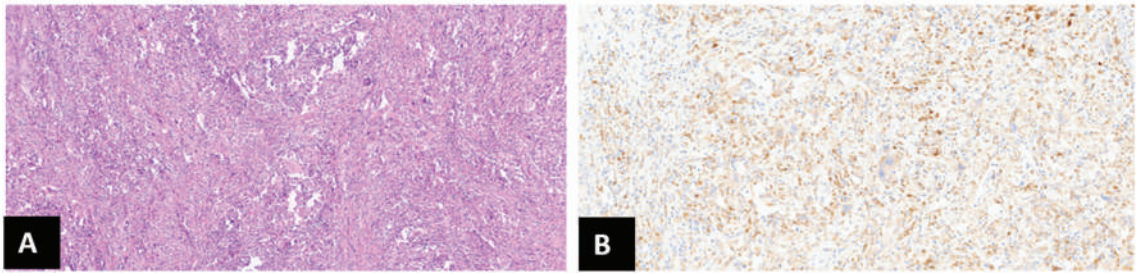

Figure 6. Histiocytic Sarcoma (HS). Hematoxylin and eosin staining (A) shows confluent sheets of discohesive, markedly atypical neoplastic cells with eosinophilic to vacuolated or xanthomatous cytoplasm, irregularly contoured nuclei and variably prominent nucleoli, and inflammation. Positive CD68 immunohistochemical stain (B) confirms the diagnosis. Cytokeratin, melanocytic markers, and B-cell and T-cell markers, and CD30 were negative, supporting the diagnosis of HS.

detect BRAFp.[39] Mutually exclusive MAPK-pathway mutations and activated (phosphorylated) ERK have been identified in almost all LCH lesions. More than 50% of cases carry BRAF mutations and 10–28% carry MAP2K1 mutation which are the major molecular alterations involved in the activation of the MAPK pathway. Other MAPK-pathway molecular alterations are BRAF exon mutations, rare BRAF alterations, and ARAF and KRAS mutations. BRAF V600E mutation is commonly present in the younger pediatric population and MAP2K1 in older children and adults.[40]

In JXG, the mononuclear, multinucleated, and spindle cells are immunoreactive for CD68, CD163, and factor XIIIa and nonreactive for CD1a, CD207 (langerin), S100, and ALK.[29] To date, there are no definitive genomic abnormalities associated with JXG. NF1 and NF2 germline mutations are found in a subset of patients indicating that there might be a constitutional predisposition to develop JXG. JXG patients with NF1 or NF2 germline mutations have been reported to have an increased risk of juvenile myelomonocytic leukemia, a myeloproliferative neoplasm of childhood associated with both germline and somatic MAPK pathway mutations.[33,41]

In *AOXG*, the foamy histiocytes are strongly positive for CD68 (Figure 3(E)), CD163, and factor XIIIa and are typically negative for S100 (Figure 3(F)), CD1a, and CD207 (langerin). However, neither a negative factor XIIIa nor a positive S100 result could rule out the diagnosis. The lymphoid infiltration exhibits a reactive profile, with germinal centers positive for CD20 and negative for BCL2.[32,33]

In *ECD*, the histiocytes are immunoreactive for CD68, CD163, and factor XIIIa and negative for CD1a and S100. Immunohistochemistry for cyclin D1, a downstream target of the MAPK pathway, shows hyperexpression with nuclear staining in ≥ 50% of the cells. BRAF V600E is positive in 50–60% of cases.[21] Co-occurrence of ECD with LCH is found in 15% of patients with ECD.[42] Recurrent activating kinase mutations and fusions involving the canonical MAPK pathway (RAS-RAF-MEK-ERK) and PI3K-protein kinase B (AKT) pathways are frequently present. Mutations activating the MAPK pathway are found in more than 80% of patients, the BRAFV600E activating mutation in 57–70%, and MAP2K1 in almost 20%.[42] Next-generation sequencing analysis to identify MAPK/PI3K-AKT pathway alterations is an important tool for the diagnosis and subsequent targeted treatment of ECD.[42,43]

Large macrophages in *RDD* are positive for CD68 (Figure 5(E)), CD163, and S100. Cyclin D1 hyperexpression with strong and diffuse nuclear positivity is commonly observed. It has been found that hyper expression of Cyclin D1 and nuclear staining are present in ≥ 50% of the cells in 86% of the patients.[35,44] RDD cells with OCT-2 nuclear immunoreactivity (Figure 5(F)) are unique in RDD and are only rarely expressed in LCH.[35,45] MAPK/ERK pathway mutations were reported in 33% of patients with RDD, in particular KRAS and MAP2K1 mutations. Mutations in BRAF (including BRAFp.V600E), ARAF, and CSF1R are uncommon. For suspected familial RDD, the workup should include SLC29A3 and TNFRSF6 germline mutation analyses. An increase in IgG4-positive plasma cells may be seen in RDD. This finding in isolation is of limited significance; the diagnosis of IgG4-associated disease should only be considered with appropriate clinical, laboratory, and radiological findings.[46]

In the *HS*, the definitive diagnosis relies entirely on immunohistochemical markers. Malignant cells should express at least two histiocytic markers such as CD163, CD68 (Figure 6(B)), and lysozyme.[36] Immunoreactivity for PU.1, CD31, CD45, CD45RO, and CD4 is common, with variable S100 expression.[38] The following markers must be negative: Langerhans cell markers (CD1a, CD207), follicular dendritic cell markers (CD21, CD35), myeloid cell markers (myeloperoxidase, CD13), and

ALK.[36] The most frequent genomic alterations are mutations in MAPK pathway genes, including KRAS, NRAS, BRAF, MAP2K1, PTPN11, NF1, and CBL.[36] The HS may co-occur or precede lymphoid neoplasms, such as follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and B- and T-lymphoblastic leukemia/lymphoma and sharing similar molecular alterations with those malignancies.[36] Clonal immunoglobulin rearrangements, abnormal somatic hypermutation, and mutations commonly found in certain B-cell lymphomas (e.g. CREBBP and KMT2D mutations) have also been reported, suggesting a potential common origin from a neoplastic B cell in these cases.[36]

Treatment (Supplementary Table 2)

Treatment options are mostly derived from case series and generally better established in the pediatric age group.[40,47] Since they can affect many organs, a pretreatment comprehensive evaluation and investigation are required in order to select the best treatment option. Surgery, radiotherapy, systemic chemotherapy, and immunotherapy are the treatment options.

Surgery

In unifocal orbital LCH, incisional biopsy with curettage of the bone with and without intralesional injection of corticosteroid (i.e. methylprednisolone, triamcinolone) is a common treatment approach.[48,49] Complete excision with clear surgical margins is not recommended as it increases healing time, potential disfigurement, and long-term complications.[50] However, more aggressive tumor debulking may be indicated in cases with optic nerve compression or severe proptosis.[51] Repeat injection of steroid 4 weeks after the first injection has been recommended for the residual tumor.[51] Considering the complications of steroid injection and anti-proliferation, anti-apoptotic, and immunomodulatory effects of alpha interferon 2-b (IFN-α2b), intralesional injection of IFN-α2b (3 injections of 1.5 million units/0.5 ml every other day) could be an alternative treatment after the biopsy.[52] Excisional biopsy of the *AOXG/JXG* is frequently curative and systemic chemotherapy is reserved for some patients with multifocal or recurrent lesions.[17] In contrast, *ECD* shows limited benefit from surgery, even though debulking may be performed for symptomatic relief.[43] Spontaneous regression of localized RDD lesions could occur after the surgical excision, even though recurrence has been reported in 33% after the surgical excision.[53] While there is no agreed treatment strategy for the patients with *HS*, a wide local excision followed by radiation therapy and/or chemotherapy has been recommended, especially in the setting of close or positive margins.[25,54]

Radiation therapy

Radiation therapy is an alternative to steroid injection after the surgery for the LCH bone lesions, especially in refractory case.[55] A complete response rate of 77% with no adverse events at a median follow-up of 54 months was reported in 80 patients with a median total dose of 15 Gy (range 3–50.4 Gy) and a dose per fraction of 2 Gy (range 1.8–3 Gy).[56] Low-dose radiation (7–10 Gy) therapy can also be considered for isolated bone lesions.[56] Newer case reports have shown the benefit of single fraction conformal radiation and stereotactic radiosurgery.[57] The type, dose, and fractionation vary significantly based on the distance of an orbital LCH from the optic nerves and chiasm.[57] When considering the treatment of pediatric populations, long-term sequelae of radiation such as dry eye syndrome, early cataract formation, optic neuropathy, radiation retinopathy, and the long-term risk of secondary malignancy are a significant factor in treatment decision-making. Therefore, radiation therapy is mostly reserved for patients with refractory or recurrent lesions.[58] Radiation in the *AOXG/JXG* is recruited for some patients with multifocal and recurrent lesions.[17] Primary and main treatment of the patients with *ECD* is systemic chemotherapy. Radiation therapy has shown a limited effectiveness in high risk RDD patients with refractory lesions threatening the vision or causing airway obstruction.[53] Although no standardized radiation dose exists, doses between 30 and 50 Gy have been reported.[53] Radiotherapy and chemotherapy are adjunctive treatments for the HS patients following a wide surgical excision.[59,60]

Systemic chemotherapy

LCH patients with multi-organ involvement respond well to systemic chemotherapy.[40] It is better established in the children than adults. The LCH-III trial showed that children treated with 12-month vinblastine and prednisone had a significantly ($p = 0.03$) higher rate of progression-free survival (54%) than 6-month course (37%).[61] A higher dose of the same medications for 12 months is used for the pediatric patients with multisystem LCH.[55] In addition, cytarabine in combination with intravenous immunoglobulin or vincristine demonstrated therapeutic potential in children and young adults with central nervous system LCH.[40,61] Evidence supporting the use of conventional chemotherapies in adult LCH is from a few case

series.[62,63] A combination of cytarabine and methotrexate in adult patients with multisystem or multifocal LCH showed a 3-year event-free survival of 68%.[63] However, hematological toxicity (mostly neutropenia) was noted in 94% of patients at least once during the treatment.[63]

While surgery is the primary treatment in patients with AOXG/JXG, systemic treatment could be effective in some multifocal or recurrence disease. Recurrent AOXG occurred in two out of 6 patients with debulking surgery who were treated with prednisolone and azathioprine which led to no recurrence.[64]

Systemic interferon alpha-2a and/or pegylated interferon alpha is effective in patients with ECD.[47] In a multicenter prospective study of 53 patients with biopsy-proven ECD, 46 patients (87%) received interferon-α and/or pegylated interferon-α in whom the treatment was identified as an independent predictor of survival[43] While it was not initially recommended for the central nervous system ECD, results of several case reports and a series of 24 French patients showed improvement and stabilization of the disease.[43] Pegylated interferon alpha is available in the USA and has a better safety profile.[65] Methotrexate, cladribine, sirolimus, and prednisone have also shown some treatment effects in a few case reports.[43]

Systemic steroid resulted in 53% recurrence of RDD in 30-month follow-up.[45] Adding 6-mercaptopurine, methotrexate, or azathioprine, and rituximab to the systemic steroid led to no recurrence.[45,46] Cladribine, often used as a second-line treatment, has shown a 67% overall response rate with no relapses at 16 months.[46] Weekly rituximab for 4 weeks was used in 15 patients and led to a response rate of 64% at 24-months follow-up.[66]

Targeted therapy and immunotherapy

In LCH the mitogen-activated protein kinase (MAPK) signaling pathway plays a key role in the regulation of gene expression, cellular growth, and survival.[67] BRAF V600E mutations are found in 75% of LCH patients.[63] Phase 2 BASKET study of vemurafenib in 26 adults with BRAF V600E-mutated LCH showed an overall response rate of 61.5% and a 2-year progression free and overall survivals of 86% and 96%, respectively.[68] The most common adverse events were hypertension (27%), maculopapular rash (23%), increased lipase (15%), arthralgia (12%), hyperkeratosis (8%), and actinic keratosis (8%).[68] MEK inhibitor Trametinib and Cobimetinib have also shown to be effective in some case series.[69,70] Novel agents like TRK inhibitors Entrectinib and Larotrectinib have shown promising results in the treatment of LCH as a part of the BASKET trial for solid tumors with NTRK fusions.[71] *ECD* shares similar molecular targets. The VE BASKET trial results led to FDA approval of vemurafenib in 2017.[72] Dabrafenib, another BRAF V600 E inhibitor has been shown to be effective and less toxic.[69,70] Crizotinib and selpercatinib for ECD with rearrangements in ALK and RET as well as larotrectinib and entrectinib for ECD with NTRK fusions could also be potential treatments due to the presence of mutation PIK3CA in ECD.[43] Targeted therapies is less established in RDD. While the BRAF V600E mutation is uncommon in RDD, other mutations in the MAPK/ERK pathway have been identified as potential targets for treatment.[46,47] Cobimetinib in cases with KRAS mutations and the MEK inhibitor trametinib (regardless of molecular profile) have shown some treatment responses.[47]

Follow up

Late-onset complications of LCH are neurodegenerative changes described as cerebellar ataxia, pyramidal tract involvement, neuropsychological impairment, and pseudobulbar palsy.[73] In a prospective study of 671 pediatric patients, a 10-year neurodegenerative risk of 7.8% and 0% were observed in patients with and without pituitary, skull base or orbital bone involvement, respectively.[73] Surveillance after completion of treatment with PET scan and MRI of the orbit and brain is recommended every 3 to 6 months for the first 2 years and then at least annually.[40]

The same follow-up imaging has been recommended for all the head and neck histiocytic lesions, and Systemic chemotherapy is the mainstay of treatment for the recurrent histiocytic lesions.[15,17,32,40,46]

Conclusion

This review places much emphasis on the complexity of these tumors and their requirement for a uniform diagnostic and therapeutic approach. Diagnosis of different periocular histiocytic lesions (Supplementary Table S1) is based on detailed histological characteristics (Table 1) and presence or absence of tumor markers on immunohistochemical staining (Table 2). Treatment options (Supplementary Table S2) vary depending on the type of histiocytic lesions, number of lesions, number of involved organs, and presence of vital organ involvement such as central nervous system. Surgical (debulking) biopsy is the first diagnostic step for all and serves as the main treatment for LCH and XG. Patients with EDC, RDD, and HS require

Table 1. Histopathological characteristics of the common orbital histiocytic disorders.

	Common findings on Hematoxylin and Eosin staining	Characteristic feature
LCH	• Large histiocytes (10–25 μm): Round to oval with nuclear grooves. • Eosinophilic cytoplasm • Inflammatory infiltrate: Eosinophils & lymphocytes (plasma cells are rare). • No mitotic activity or nuclear pleomorphism.[27]	• Fibrosis gradually replaces Langerhans cells & inflammatory infiltrate. • As fibrosis increases, diagnosis becomes more difficult.[27]
JXG	• Three cell types: Mononuclear cells, Multinucleated cells (with/without Touton giant cells), Spindle cells[28] • Early lesions: Mixed histiocytes, lymphocytes, plasma cells, neutrophils, eosinophils.[30] • Mature lesions: Foamy histiocytes with Touton giant cells (85% of cases).[31]	• Touton giant cells are rare in orbital/intraocular JXG. • Late-stage JXG: Fibrosis and fibroblast proliferation. • Adult JXG (<10% of cases): Can resemble AOXG.[31]
AOXG	• Foamy histiocytes (Xanthoma cells) in orbicularis muscle & orbital tissue • Dispersed or clustered lymphocytes, plasma cells, and Touton giant cells • Lymphoid follicles with reactive germinal centers.[32–34]	• Fibrosis is present to varying degrees. • Orbital fat necrosis is frequently seen.[33,34]
ECD	• Nodular/diffuse sheets of lipid-laden or eosinophilic histiocytes with xanthomatous features • Touton-type giant cells are commonly seen. • Background stroma: Nodular lymphoplasmacytic aggregates with moderate-to-marked fibrosis (no germinal centers).[21]	• Histological overlap with LCH. • 15% of ECD cases co-occur with LCH.[21]
RDD	• Macrophages with large ovoid nuclei & prominent nucleoli. • Classic emperipolesis (lymphophagocytosis). • No xanthomatous features. • Fibrous septa separate inflammatory infiltrate.[35]	• Delicate branching capillary pattern, cuffed by plasma cells. • Emperipolesis is a key diagnostic feature.[35]

LCH: Langerhans cell histiocytosis; JXG: Juvenile xanthogranuloma; AOXG: Adult-onset xanthogranuloma; ECD: Erdheim-Chester disease; RDD: Rosai-Dorfman disease.

Table 2. Immunohistochemical characteristics of the common orbital histiocytic disorders.

	LCH	JXG	AOXG	ECD	RDD
Factor XIIIa	–	+ | –	+ | –	+	+ | –
CD68	+	+	+	+	+
CD163	– |+	+	+	+	+ | –
S100	+	– |+	– |+	– |+	+
CD1a	+	–	–	–	–
Langerin	+	–	–	–	–
OCT2	– |+	–	–	–	+
Cyclin D1*	+	+	–	+ | –	+
$BRAF^{V600E}$**	+ | – (~60%)	–	–	+ ‡| §– (~50%)	Rare

*.Nuclear strong/weak cytoplasmic blush; overexpression (nuclear staining in ≥ 50% of lesional cells).[21,33,35,38,44]
†.Cytoplasmic granular staining.
‡.AOXG: Adult-onset xanthogranuloma; ECD: Erdheim-Chester disease; JXG: Juvenile xanthogranuloma; LCD: Langerhans cell histiocytosis; RDD: Rosai-Dorfman disease kers, and CD30 were negative, supporting the diagnosis of HS.
§.| +: More commonly negative; + | –: More commonly positive. [21,30,40,42,63,68]

additional systemic chemotherapy and or radiotherapy. Systemic chemotherapy is the primary treatment for EDC, RDD, and HS. It is also the treatment of choice for the patients with multifocal or multi-organ involvement as well as recurrent or refractory lesions, regardless of the histiocytic type. Therefore, all the patients with any type of histiocytic lesion should be referred to an oncologist for further investigation and possible chemotherapy. Radiotherapy is an adjunctive primary treatment for the patients with HS. It is, however, reserved for recurrent or refractory lesions in the other types of histiocytic lesions. Targeted therapy is currently in progress and may replace the systemic chemotherapy in patients with primary LCH, ECD, and RDD. Follow-up with imaging every 3 to 6 months for the first 2 years and then annually is recommended for the patients with histiocytic lesions. Optimal patient care requires multidisciplinary collaboration between the medical and surgical oncologist, ophthalmologist, pathologist, radiologist, and radiotherapist.

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Recent Advances in Orbital Tumors—A Review of Publications from 2014–2016

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Abstract: The aim of this review article is to provide an update of the current literature on orbital tumors. The authors conducted a PubMed literature search of English language articles published between January 2014 and December 2016 using the following search items: orbit, tumors, lacrimal gland, lymphoma, hemangioma, lymphangioma. The authors included reviews, original articles, case series, and case reports with relevant new information. There is new information about the clinical spectrum of orbital tumors, capillary hemangioma, cavernous hemangioma, lymphangioma, orbital venous malformation, lacrimal gland tumors, and orbital lymphoma. This review highlights the current understanding, practice, and guidelines in the diagnosis and management of common tumors of the orbit.

Key Words: orbit, eye, tumors

(Asia-Pac J Ophthalmol 2017;6:153–158)

Orbital tumors form a very broad and a diverse spectrum, which varies based on several demographic attributes and the referral pattern. Bonavolonta et al[1] analyzed 2480 orbital space occupying lesions in their retrospective review and found that the most common benign lesions were dermoid cyst (14%) and cavernous hemangioma (9%). In the same series, non-Hodgkin lymphoma was the most common malignant neoplasm (12%). Lacrimal gland lesions were benign in 64% (154/241), whereas the most common malignant tumor was adenoid cystic carcinoma (18%).

Hassan et al[2] found that the incidence of orbital tumors in the United States according to the Surveillance, Epidemiology, and End Results (SEER) database was 1.59 per million person years. They also reported a significant increase in the overall incidence of orbital, conjunctival, and lacrimal gland tumors, with lymphoma having the highest incidence.

VASCULAR TUMORS AND MALFORMATIONS

Orbital vascular malformations are currently classified as type 1 (no flow; lymphatic vascular malformations and venous lymphatic lesions), type 2 (venous flow; distensible/nondistensible venous vascular malformations and combined distensible venous-lymphatic vascular malformations), and type 3 (arterial flow; arteriovenous malformation, cavernous hemangiomas, acquired arteriovenous shunts).

Orbital cavernous hemangioma (OCH) is the most common orbital tumor in adults and appears as a well-defined intraconal mass (Fig. 1). McNab et al[3] studied the anatomical location and laterality of OCH in 104 patients. It was found that OCH has the propensity to occur in the intraconal space (87%) and lateral to the optic nerve (47%), a distribution that mirrors the distribution of small arteries and arterioles in the orbit.

In a study of OCH in 39 patients by Rootman et al,[4] it was found that 33% of patients presented with optic nerve dysfunction, with a best-corrected visual acuity of less than 20/40 in 28%. They found that 75% of the lesions were situated in the intraconal space, with optic nerve compression in 54%. They were also found to have a dynamic imaging pattern, which helps in differentiation from other intraconal tumors. Intraconal apical OCH poses a surgical challenge with poor visual outcome. Kloos et al[5] reported 4 cases of apical pear-shaped OCH, which were partially removed leading to postoperative hemorrhage and visual loss.

Goh et al[6] reported the outcome of gamma knife radiotherapy for apical lesions, including 3 cases of cavernous hemangioma and 2 cases of schwannoma. Each patient received 2000 cGy in fractionated doses leading to tumor shrinkage with average volume reduction of 76% and improved visual acuity. Application of gamma knife can avoid surgery-related complications in visually incapacitating benign orbital lesions situated in critical locations and thus not easily amenable to surgery.

A rare entity that requires special mention is intraosseous hemangioma. Although the pathogenesis of intraosseous hemangioma is unknown, these can occur in the orbit. Gupta et al[7] reported 6 cases of histopathologically confirmed intraosseous hemangioma with characteristic "honeycomb" pattern on computerized tomography images. Charles et al[8] reported a rare case of intramuscular hemangioma in the inferior oblique that was completely excised.

Lymphangioma of the orbit is a much discussed topic. It is classified as a type 1 vascular malformation according to the International Orbital Society. Although it is a benign entity, it may progress to severe globe displacement and cosmetic disfigurement. Lymphangioma can be both microcystic (≤1 cm) and macrocystic (≥1 cm). The management of lymphangioma poses a challenge due to the diffuse nature of the tumor and the associated bleeding. Surgical debulking has been attempted after intralesional injection of fibrin glue to solidify the lesion. Recently, Gooding et al[9] reported the use of intralesional bleomycin injection attributed to its sclerosing property on vascular endothelium and chemical pleurodesis. They injected a dose of 1 IU bleomycin in

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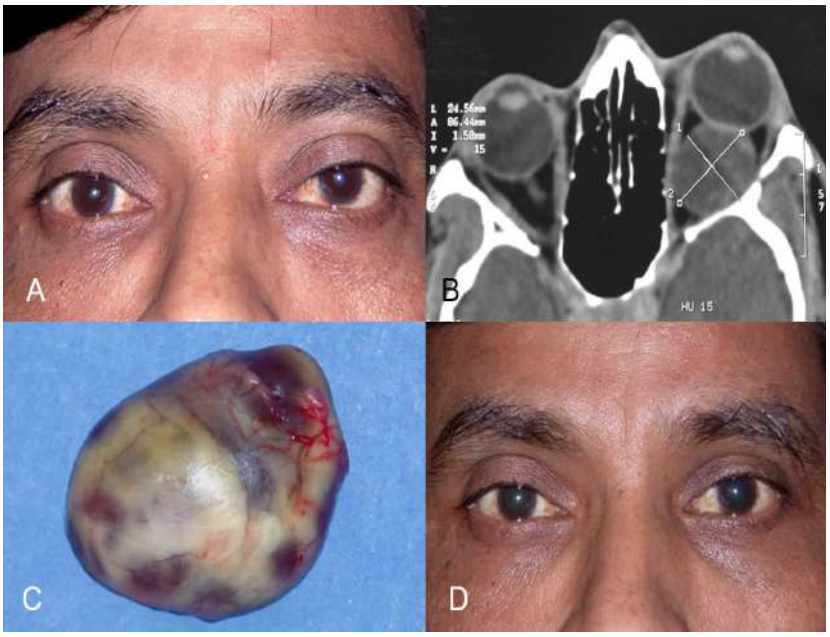

FIGURE 1. A 40-year-old male presenting with painless proptosis of the left eye with normal visual acuity (A). Computed tomography (CT scan) imaging showing a well-defined homogenous spherical intraconal mass (B), which was excised by lateral orbitotomy (C) and histopathology confirmed cavernous hemangioma. The patient did well postoperatively (D).

1 mL and lignocaine in the ratio of 4:1 under direct visualization using a 23-gauge needle, with marked clinical improvement and only transient side effects. The amount injected was equivalent to the volume of the lesion, not exceeding 5 mL; the number of injections ranged from 1 to 6 (Fig. 2).

The role of pingyangmycin was evaluated for low-flow orbital venous malformations by Jia et al.[10] Pingyangmycin belongs to the bleomycin family, also known as bleomycin A5, and was initially discovered in the Pingyang county of China. Of the 33 eyes treated, the majority were situated in the eyelid (52%), followed by the conjunctiva (27%), intraconal space (12%), glabella (6%), and inner canthus (3%). There was a mean decrease in volume of 84% (range, 28% to 100%) with a median number of 2 injections (range, 1 to 4) at an interval of 6 to 8 weeks, and there was no recurrence at a mean follow-up of 8 months. Similar results were reported by Yue et al[11] in 13 patients with venous malformation (n = 6), cavernous hemangioma (n = 6), and lymphangioma (n = 1). Injection was performed under direct observation in all except one and the mean dosage was 4.2 mg (range, 2 to 6 mg). The average reduction of volume was 70% without associated complications except for transient swelling. It was found to be safe and effective.

Gandhi et al[12] reported the use of oral sildenafil (1 to 3 mg/kg) in divided doses in 2 children with orbital lymphangioma. The proposed mechanism is smooth muscle relaxation and collapse of cystic spaces of the lesion. Oral sildenafil is considered as a promising treatment in lymphangioma, although larger clinical trials may provide further details. Sclerotherapy with sodium tetradecyl sulphate is still considered as a management option in macrocystic lymphatic malformations. The outcome in 29 patients who underwent primary sclerotherapy (n = 18) and secondary treatment (n = 11) was encouraging with radiological resolution in 52%.[13]

Infantile hemangioma is a congenital, self-limiting benign disease that is characterized by a proliferation phase and an involution phase. However, occasionally orbital infantile hemangioma may cause functional impairment as a result of proptosis, compressive optic neuropathy, and amblyopia. Levitt et al[14] reported 5 cases of orbital infantile hemangioma treated with oral propranolol (0.6 to 2.7 mg/kg). Maximal therapeutic effect is noticed during the proliferative phase (Fig. 3). There was significant clinical and radiological improvement in all the cases.

FIGURE 2. An 8-year-old child with mild proptosis of the left eye of 3 months' duration with acute exacerbation after minor trauma (A). CT scan showed a diffuse orbital mass. Intraoperative histopathology confirmed lymphangioma. The child did very well after intralesional bleomycin injection (B).

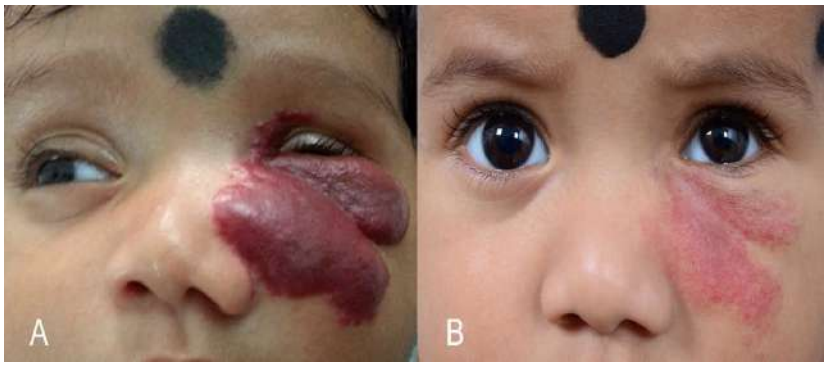

FIGURE 3. Capillary hemangioma of infancy in the left eye with anterior orbital extension in the rapid proliferative phase in a 3-month-old child (A), which substantially involuted after oral propranolol 2 mg/kg per day in 2 divided doses for 3 months (B).

Recently, Painter and Hildebrand[15] reported promising results of topical timolol 0.5% in 5 children with deep periocular infantile hemangioma.

Carotico-cavernous fistula (CCF) is an abnormal vascular communication leading to rapidly progressive orbital symptoms and signs. Often, the related ocular complications of CCF are mainly due to orbital congestion, vascular occlusion, and optic nerve compression. Various classifications of CCF are direct and indirect, high flow and low flow, spontaneous and traumatic. Angiographically, they are classified as anterior and posterior. Ocular involvement was found to be associated with anterior draining dural CCF. Tan et al[16] evaluated 45 patients with CCF. It was found that 18% had direct CCF and 82% were indirect. The majority (88%) had traumatic etiology in direct CCF, whereas hypertension (41%) and hyperlipidemia (46%) were the cause for indirect dural CCF. The major statistically significant risk factors associated with poor prognosis were the use of anticoagulants and visual acuity less than 6/60.

SOLITARY FIBROUS TUMOR

Orbital solitary fibrous tumor, a rare spindle cell tumor, has been gaining attention recently. Clinically this may present as a well-defined intra- or extraconal mass simulating cavernous hemangioma, schwannoma, meningioma, or fibrous histiocytoma (Fig. 4). Immunohistochemistry is the major diagnostic tool to differentiate it from aggressive hemagiopericytoma. It is found to exhibit strong immunoreactivity for CD34 (90–100%) and CD99 (70%). Le et al[17] reported 4 cases of orbital solitary fibrous tumor, which were indolent in nature without recurrence after complete excision.

LACRIMAL GLAND TUMORS

A histopathological survey of lacrimal gland tumors was performed at a tertiary hospital in Singapore. The series comprised a majority of patients of Chinese ethnicity. Chronic dacryoadenitis

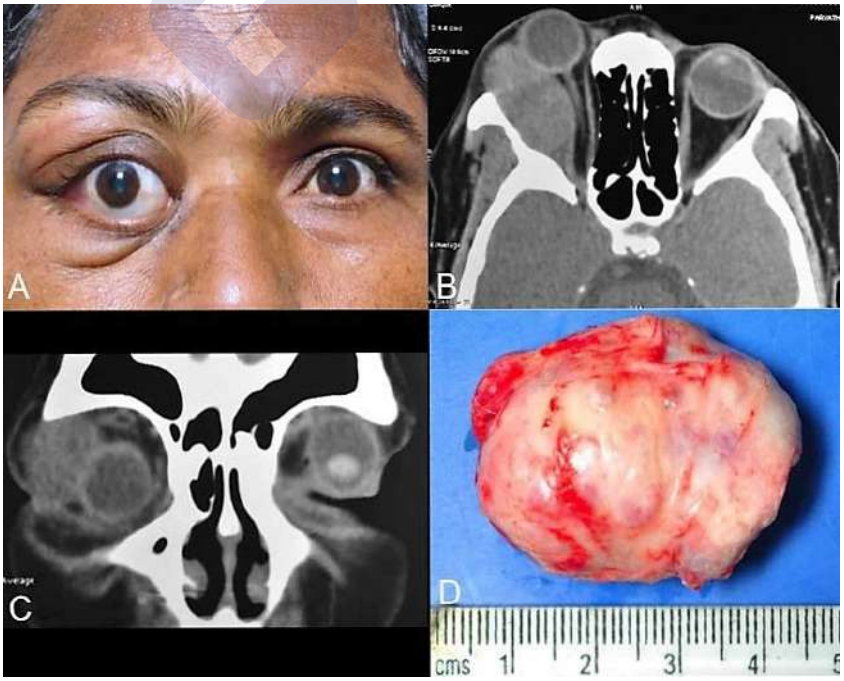

FIGURE 4. A 52-year-old Indian female showing proptosis of the right eye with inferomedial globe displacement (A). The CT scan was suggestive of a well-defined large orbital mass occupying the superolateral orbit extending beyond the mid-orbit pushing the optic nerve medially. Lacrimal gland could not be seen separately (B, C). It was completely excised surgically and appeared as a well-encapsulated mass; it was diagnosed to be solitary fibrous tumor of the orbit on histopathology (D).

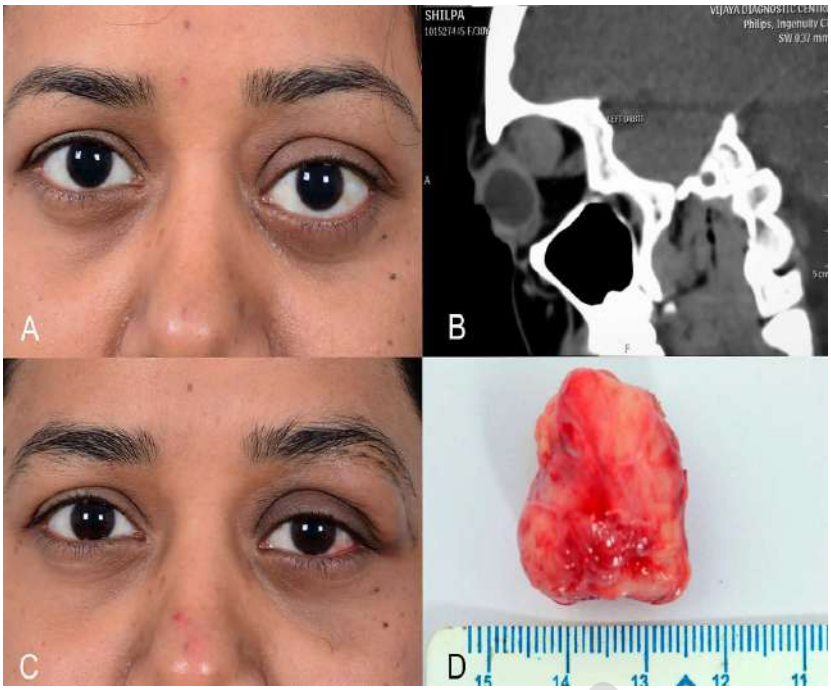

FIGURE 5. A 30-year-old female with proptosis of the left eye with downward displacement (A). CT scan showed a well-defined mass in the lacrimal gland (B), which was completely excised (C) with histopathological confirmation of pleomorphic adenoma (D). The patient did well with resolution of proptosis postoperatively.

and lymphoproliferative disorders were the 2 most common lacrimal gland lesions in the series. Of the 69 patients, adenoid cystic carcinoma was found only in 1. Tang et al[18] retrospectively evaluated bilateral lacrimal gland diseases in 97 patients and found that idiopathic orbital inflammatory disease was the most common in etiology (30%) and lymphoma accounted for only 11%.

Dacryops and its pathogenesis is less understood. It is generally classified as palpebral, orbital, and Krause dacryops. Lam et al[19] in their recent series analyzed 5 specimens of excised dacryops histopathologically. They confirmed that cyst formation was due to chronic inflammation and immune response activating the local plasma cells to produce IgA that accumulates, resulting in osmotic effect and cyst formation.

Chawla et al[20] studied a case series of 66 epithelial tumors of the lacrimal gland that comprised benign pleomorphic adenoma in 76% (Fig. 5) and malignant in 24%. Adenoid cystic carcinoma (ACC) was the most common malignant tumor with a mean age at presentation of 32 years. Other malignant tumors included carcinoma ex-pleomorphic adenoma, lacrimal duct carcinoma, mucoepidermoid, and basal cell adenocarcinoma.

Gensheimer et al[21] reported the outcome of neutron radiotherapy in 11 eyes with ACC. By Kaplan-Meier analysis, 5-year local tumor control was 80%, disease-free survival was 61%, and overall survival was 90%. However, late recurrences and distant metastasis were a challenge. Of the 11 patients, 3 had local recurrence and 4 developed distant metastasis. The median radiation dose was 18.4 neutron Gy. Neutron radiotherapy carries the advantage of reduced dose and fractions of radiation delivery compared with conventional radiation. Holliday et al[22] reported the use of proton beam therapy in malignant epithelial tumors of the lacrimal gland with limited toxicity at a median radiation dose of 60 Gy. They limited the maximum corneal dose to 35 Gy with an eye deviation technique.

Tse et al[23] reported the long-term results of intra-arterial cytodestructive chemotherapy (IACC) with cisplatin and doxorubicin in ACC of lacrimal glands in 19 patients. In their study, IACC was administered in addition to orbital exenteration, chemoradiation, and systemic chemotherapy. They found an overall improved survival in patients receiving neoadjuvant IACC. Bell et al[24] found that *KRAS*, *NRAS*, and *MET* mutations were frequent in epithelial neoplasms in the lacrimal gland, especially in ACC, which can pave the way for newer targeted therapies. Of the 16 patients with ACC studied, 44% had these oncogenic mutations.

OCULAR ADNEXAL LYMPHOMA

Ocular adnexal lymphoma (OAL) is a malignant lymphoproliferative neoplasm involving the eyelid, conjunctiva, orbit, and lacrimal gland, comprising 30% of orbital tumors (Fig. 6). It is often low-grade non-Hodgkin B-cell lymphoma. Of the OALs, extra-marginal zone lymphoma (EMZL) or mucosa-associated lymphoid tissue (MALT) lymphoma are most common (50% to 90%) and have better prognoses. Other types are follicular cell, mantle cell, diffuse large B-cell (DLBCL), and lymphoplasmacytic lymphoma. Rasmussen et al[25] performed a multicenter collaborative study on ocular adnexal follicular lymphoma (FL) from 6 ocular oncology centers around the world. Of the 98 patients included in the study, 70% had primary, 19% had associated systemic involvement, and 10% had ocular adnexal relapse. The most frequently involved sites were the lacrimal gland, conjunctiva, and orbit. On staging the disease, it was found that TNM staging was not consistent with disease progression and survival. Overall survival was 60% and 20% at 10 and 20 years, respectively. External beam radiotherapy alone as a treatment modality in FL showed favorable outcome with a disease-specific survival rate of 94% at a median dose rate of 26 Gy. In another study,

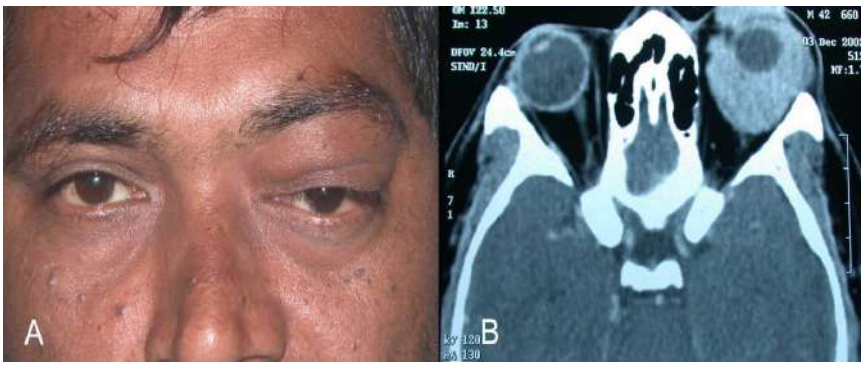

FIGURE 6. A 40-year-old male presented with mild slowly increasing proptosis of the left eye for 1 year (A). CT scan shows an isodense mass molding around the eye (B) suggestive of orbital lymphoma, which was confirmed on incisional biopsy.

Rasmussen et al[26] analyzed the clinicopathological aspects of OAL. Diffuse large B-cell lymphoma is an aggressive variant that accounts for 8–13% of lymphoma overall. They identified 34 patients with DLBCL with a median age of 78 years. Primary DLBCL occurred in 53% and orbit was the site of involvement. It was unilateral in 97%. The prognosis correlated with Ann Arbor classification; the higher the stage, the poorer the prognosis. Histopathologically, they were categorized as centroblastic and immunoblastic; immunoblastic had poorer prognosis in terms of overall survival. The overall 5-year survival rate was 20% in their study population, much lower than previously reported.

Until recently, OAL was staged according to the Ann Arbor classification system, originally designed for Hodgkin lymphoma. The recent introduction of the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging in OAL has been elaborately analyzed by various authors. Rath et al[27] analyzed 134 cases of OAL based on AJCC TNM staging and grouped the tumors according to laterality, along with nodal and systemic metastasis: group 0, unilateral OAL with no nodes or metastasis; group 2, either bilateral or positive nodes/metastasis; group 3, both bilateral OAL and positive nodes/metastasis. It was found that 10-year progression-free survival was 75%, 50%, and 0% in groups 0, 1, and 2, respectively.

Aronow et al[28] studied the current AJCC TNM staging in 63 patients with OAL. They found that although the TNM staging system was useful for precise characterization of local extent of tumor, it was not appropriate to predict recurrence or survival. In contrast, Sneigowski et al[29] in their evaluation of the prognostic significance of AJCC TNM staging of OAL in 82 patients found that higher staging was associated with decreased 5-year disease-free survival. The prognosis and survival in OAL depends on the histologic subtype, laterality, and systemic involvement.

Takahashi et al[30] identified a high-resolution single nucleotide pleomorphism array that could detect choromosomal abnormality patterns in ocular adnexal lymphoma to differentiate it from benign lyphoproliferative disorders. Radiotherapy is the current standard of care in OAL locally, irrespective of the subtype, and is considered safe and effective. Woolf et al[31] showed excellent tumor control (100%) in 85 eyes with a median fractionated dose of 30 Gy. Local tumor control at 5 years was reported as 98% by Kharod et al[32] with 25.5 Gy in 44 patients.

Rituximab, a chimeric monoclonal antibody directed against B-cell–specific CD20, has recently gained popularity in the treatment of non-Hodgkin B-cell lymphoma. Tuncer et al[33] evaluated the therapeutic efficacy of rituximab in 10 patients with OAL, of which 4 had orbital involvement. Overall, complete response was achieved in 36% (n = 4) and the remainder required adjuvant radiotherapy for recurrence. In the presence of systemic involvement, it plays a major role.

ORBITAL INVASION OF BASAL CELL CARCINOMA

Oral vismodegib, the hedgehog pathway inhibitor, has gained popularity recently in treating syndrome-associated and locally advanced/orbital basal cell carcinoma (BCC). There are case series and isolated case reports on the outcome and complications. Gill et al[34] evaluated the response and complications of 150 mg oral vismodegib in 7 patients with locally advanced BCC. At a mean treatment duration of 11 weeks (range, 4 to 16 weeks), 58% had 80–100% regression, 29% had less than 35% partial regression, and there was progression in 1 patient (14%). Of the 7 patients, 6 had adverse reactions including alopecia (29%), muscle cramps (29%), and dysgeusia (29%). Occurrence of new squamous cell carcinoma was observed in 2 patients after completion of treatment. Ozgur et al[35] recently reported 12 patients with locally advanced BCC and treatment outcome with vismodegib, of which 3 had complete response and 2 had progressive disease after complete response. The most common drug-related toxicities were muscle spasms (100%) and weight loss (83%). Although vismodegib is an accepted novel therapeutic option in BCC, side effects and long-term outcome need further validation.

CONCLUSIONS

Knowledge of orbital diseases and their management has continued to evolve in the past year. We have valuable new information about orbital venous malformation, lacrimal gland tumors, and orbital lymphoma. Advanced basal cell carcinoma with orbital extension now has a conservative medical treatment.

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