Case Report: Primary Squamous Cell Carcinoma of the Orbit in a patient with Carney's syndrome treated with multidisciplinary approaches

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Abstract

Introduction: Squamous cell carcinoma (SCC) is a rare malignancy of invasive epithelium with keratinocyte differentiation, and it is the most common form of eyelid malignant neoplasm, comprising 5-10% of malignancies. While SCC rarely affects the orbit, it may be involved through local invasion from a cutaneous primary site or extension by perineural invasion. Only 11 cases of primary orbital SCC have been reported until now. Here, we present a case of primary carcinoma of the right orbit with coexisting Carney's syndrome, a rare genetic disorder associated with multiple endocrine neoplasias (MEN) syndromes. **Case:** A 62-year-old south Asian male presented with a painful swelling in the lateral aspect of the right eyebrow and protrusion of the eyeball in August 2020. He had a history of excision of Right atrial Myxoma in March 2020. Orbital computerized Tomography (CT) and Positron Emission Tomography (PET-CT) scans revealed an enhancing soft tissue lesion in the right orbit with involvement of frontal and ethmoid sinuses. Biopsy confirmed HPV related poorly differentiated squamous cell carcinoma, positive for HPV-related markers. The patient received concurrent chemo irradiation with Cisplatin. Follow-up done PET-CT done 3 months later showed a new lesion appeared in the right orbital region and right lobe of thyroid. Later had surgical excision and total thyroidectomy and Histopathological examination (HPE) from orbit was reported as invasive SCC and from the thyroid was reported as synchronous papillary thyroid cancer. The patient's proptosis resolved, and subsequent PET-CT and Magnetic Resonance Imaging (MRI) scans did not show any residual or recurrent disease. **Conclusion:** Primary SCC of the orbit is an extremely rare disease, and this case report presents the 12th reported case and the first one associated with Carney's syndrome. As there is no standard treatment regimen for primary SCC of the orbit, this case highlights the use of multimodality treatment, including surgical excision and chemo irradiation. The findings emphasize the importance of early detection and management of this uncommon and life-threatening condition, providing hope for patients and aiding in the prevention of recurrence.

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Keywords: Primary Orbit Cancer, Squamous Cell Carcinoma, Cardiac Myxoma, Papillary Carcinoma of Thyroid, Carney's syndrome

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Abstract:

Introduction:

Squamous cell carcinoma (SCC) is a rare malignancy of invasive epithelium with keratinocyte differentiation, and it is the most common form of eyelid malignant neoplasm, comprising 5-10% of malignancies. While SCC rarely affects the orbit, it may be involved through local invasion from a cutaneous primary site or extension by perineural invasion. Only 11 cases of primary orbital SCC have been reported until now. Here, we present a case of primary carcinoma of the right orbit with coexisting Carney's syndrome, a rare genetic disorder associated with multiple endocrine neoplasias (MEN) syndromes.

Case:

A 62-year-old south Asian male presented with a painful swelling in the lateral aspect of the right eyebrow and protrusion of the eyeball in August 2020. He had a history of excision of Right atrial Myxoma in March 2020. Orbital computerized Tomography (CT) and Positron Emission Tomography (PET-CT) scans revealed an enhancing soft tissue lesion in the right orbit with involvement of frontal and ethmoid sinuses. Biopsy confirmed HPV related poorly differentiated squamous cell carcinoma, positive for HPV-related markers. The patient received concurrent chemo irradiation with Cisplatin. Follow-up done PET-CT done 3 months later showed a new lesion appeared in the right orbital region and right lobe of thyroid. Later had surgical excision and total thyroidectomy and Histopathological examination (HPE) from orbit was reported as invasive SCC and from the thyroid was reported as synchronous papillary thyroid cancer. The patient's proptosis resolved, and subsequent PET-CT and Magnetic Resonance Imaging (MRI) scans did not show any residual or recurrent disease.

Conclusion:

Primary SCC of the orbit is an extremely rare disease, and this case report presents the 12th reported case and the first one associated with Carney's syndrome. As there is no standard treatment regimen for primary SCC of the orbit, this case highlights the use of multimodality treatment, including surgical excision and chemo irradiation. The findings emphasize the importance of early detection and management of this uncommon and life-threatening condition, providing hope for patients and aiding in the prevention of recurrence.

Introduction:

Primary Orbital squamous cell carcinoma is an exceedingly rare condition. This is mainly due to absence of native squamous epithelium of the orbit itself. SCC is the most common form of eyelid malignant neoplasm comprising 5-10% malignancies. It mainly affects older patients between 50 to 75 years. Moreover, the incidence rate is very low ranging between 0.09 to 2.42 cases per 0.1 million population [1-3]. The number of reported cases of orbital squamous cell carcinoma are very few. The presenting signs and symptoms can sometimes be challenging and diagnosis is difficult. On top of that the management is also very difficult to with irradiation and organ preservation modality with dose constrain in the structures in the orbit and nearby vital structures like opposite eye, lens, retina, and optic nerve including optic chiasm. Although along with Carney's syndrome makes this case more particular and unique.

In our case, we report a case of primary carcinoma of the right orbit who had coexistent carney's syndrome. We have also described the workup, staging and multidisciplinary management for the orbital SCC.

Case Presentation:

A 62 years old south Asian gentle male [Fig: 1a], presented in Aug 2020 to an eye specialist with the complaints of painful swelling in the lateral aspect of right eyebrow with protrusion of the eyeball. He had a past history of excision of Right atrial Myxoma on March 2020 [Fig: 2a] by cardiac surgeon in United Hospitals Limited, Dhaka, Bangladesh. On examination, he had proptosis, the mass was fixed to skin, and it was tender. Orbital CT showed an enhancing soft tissue lesion measuring 3.2 x 3 cm in the superior-medial aspect of the right orbit with orbital roof and medial nasal bone erosion and extension to frontal sinus and anterior ethmoid sinus, the lesion was extraconal and was abutting the superior rectus and was compressing the right globe & the lacrimal gland was not involved. Staging PET-CT showed a hypermetabolic soft tissue mass in the superior-medial aspect of right orbit (SUV max 19.95) involving the right frontal sinus & eroding the roof of right orbital bone extended to ethmoidal sinus suggesting malignancy [Fig: 1c]. PET also revealed a hypermetabolic soft tissue nodule in the right lobe of thyroid (SUVmax - 13.4) [Fig: 1d]. PET scan did not reveal any distal metastases in lung or liver or bone or in any lymph nodes.

He had an incisional biopsy from the right orbital mass at Bangladesh Eye Hospitals by Eye surgeon and histopathology [Fig: 2a] was reported as poorly differentiated squamous cell carcinoma. The slides and block were send for a second opinion to another pathologist who confirmed the diagnosis. The orbital mass was found to be CK5/6-Positive [Fig: 2c], p16-positive [Fig: 2d], p63-positive [Fig: 2e] and was reported as HPV related squamous cell carcinoma. FNAC from the hypermetabolic thyroid swelling was suggestive of papillary thyroid carcinoma. His Postoperative MRI [Fig: 1b] in Sep 2020 showed a large heterogenous mass (AP 3.6 x TD 4.6 X CC 3.3 cm) in the superior – medial region of right orbit with extension into right frontal sinus and right ethmoid sinus. The superior rectus muscle was involved, and the apex was free of tumor. There was significant proptosis due to mass effect.

His case discussed in a multidisciplinary team (MDT) at Bangladesh Specialized Hospital Limited owing to rarity of diagnosis and it was decided to offer him concurrent chemo irradiation with Cisplatin in view of organ preservation aspect. Radiotherapy was delivered at Delta Medical College Hospital, Dhaka, Bangladesh by Rapid arc technique with Varian True beam machine (Version 2.7) with dose of 56 Gy [Fig: 1g] was delivered in 28 fractions that is 200 cGy per fraction along with 6 doses of concurrent cisplatin (30mg/m2) with dose of 40mg weekly schedule. He required adaptive re-planning as he had shrinkage in his orbital swelling while on

treatment. His concurrent Chemo Radiotherapy (CCRT) was completed in October 2020. We have observed the Dose Volume Histogram (DVH) and the Max Dose (cGy) in PTV-56 6049.1 and other organ at risk (OAR) like Brain Steam 2174.7, Cochlea Left 141.4, Cochlea Right 639.5, Eye Left 889.1, Eye Right 5983.7, Lens Left 252.1, Lens Right 5346.1 Left, Optic Chaism 3688.1, Optic Nerve Right 5976.2, Optic Nerve Left 2203.5 & Pituitary 2992.4.

He developed an exophytic growth in the lateral aspect of right orbit, three months' post completion of CCRT and a repeat PET CT [Fig: 1e] showed a 19 x 13 mm hypermetabolic (SUV max 11.25) lesion in the right anterior lateral angle of the orbit. The frontal sinus, superio-medial aspect of right orbit, ethmoid sinus showed no uptake confirming the good response to CCRT. There was persistence of hypermetabolic lesion in the right lobe of thyroid (SUVmax 13.12). His case was re-discussed in MDT, and he underwent excision of the new lesion in the right orbital region along with reconstruction, Right eye tarsorrhaphy and Total thyroidectomy in Jan 2021 at Square Hospitals Limited. The HPE showed invasive squamous cell carcinoma of the right orbit with deep margin involvement. The bone was involved by tumor and the tissue from the frontal sinus was uninvolved. The total thyroidectomy specimen was consistent with papillary carcinoma of thyroid of the right lobe [Fig: 2f] (Size 2cm, margins clear, 1 LN with tumor, LVSI present – pT1N1aMx).

At his last follow in June 2023 up his vision is near normal in left eye and poor vision in Right (Finger counts), proptosis had resolved, and his last 3 consecutive PET CT [Fig: 1f] & MRI (last on December 2023) did not show any residual or recurrent disease [Fig: 1h].

Discussion:

Squamous cell carcinoma of the orbit is an extremely rare disease and till date 11 cases have been reported so far. Our case is the 12^{th} case and first case in a patient with carney's syndrome (Table 1). However, it is progressive and life-threatening. Mr. Kaiser, our patient, male, 62 years old, a case of carcinoma of right orbit with bone erosion and frontal and ethmoidal sinus involvement. The patient visited with burning sensation, itching and watering from both eyes. On examination, we found a painful swelling in lateral side of right eyebrow and protrusion of the same eyeball. A case report in 2012 by Peckinpaugh JL. et al. mentioned a patient, male, 63 years old, visited with the symptoms of diplopia, ophthalmoplegia, eye pain and forehead numbness [5]. In our case, the soft tissue mass measured 3.2 cm in the superior-medial aspect of the right orbit, lesion was extraconal abutting superior rectus muscle and compressing right globe which abuts the sclera. A similar case report in 2017 by Campos Arbulu et al. where the patient was 73 years old, and the lesion was around 3.5 cm, located in superior orbit abutting the frontal sinus [6]. Another report in 2012 by Peckinpaugh JL et al. had a female patient, 43 years old, whose lesion's size was not reported, but located in the orbital apex [5].

Diagnosis was based on clinical examination as well as modalities like CT-Scan, PET CT-Scan, excision biopsy, etc. Another case report in 2011 by Saha et al. detected the disease based on MRI of brain, orbit, sinus (initially negative) repeats MRI brain, orbit 1 year later, excisional biopsy via trans frontal craniotomy, and systemic evaluation by clinical oncologist [7].

The challenge in management of SCC of orbit includes inoperability or complete excision. In our case bone erosion was present and radiotherapy dose escalation up to 60-66Gy [8] despite needs of SCC due to constrains is also challenging, but we are able to deliver only 56Gy in our case. Appropriate guidelines of concurrent chemo are not established and no evidence of neoadjuvant treatment reported.

Treatment for papillary cancer and follow-up is also difficult. Treatment modalities included excision of right atrial myxoma, excision biopsy, concurrent chemo radiotherapy followed by plastic surgical reconstruction due to recurrence and total thyroidectomy for synchronous papillary thyroid cancer. Another case report by Blandford et al., in 2018, male patient, 63 years of age, was treated with right orbitotomy with excisional biopsy, orbital chemoirradiation [9]. In this case for recurrence surgery was challenging in view of local failure and organ preservation, so plastic and reconstructive surgeons who able to do a prefect surgery for the residual disease in combination with ENT & head neck surgeons of the Thyroid. Post excision biopsy showed of bone invasion and deep margin involvement and adjuvant further treatment option also again challenging despite

of ypT4 disease with high garde-3. Short duration of radiotherapy interval & re-radiation with conventional proton was also an option but MDT decided for observation rather further adjuvant treatment.

Carneys complex is a rare genetic disorder associated with MEN syndromes and it affects multiple glands in the body such as thyroid, pituitary and adrenal glands. It also causes cardiac myxomas. [10]. Another important learning point in this case was that the patient had atrial myxoma, orbital SCC and papillary carcinoma of the thyroid almost at the same time. He had fulfilled two of the major criteria required for the diagnosis of carneys complex [11]. Carney's complex predisposition to developing multiple neoplasms, necessitating regular follow-up and early screening for new tumors.

As per our knowledge, this case is the first which reports the development of orbital squamous cell carcinoma in a patient with carneys complex. The implication of knowing about the carneys complex is that this patient is predisposed to development of multiple neoplasms in future, and he needs to be followed up regularly and screened for early identification of new tumors. Mutations in the protein kinase A type I alpha regulatory subunit (PRKAR1A) needs to be identified in patient and his potentially affected at risk family members [12]. This patient has not been tested for any mutations as we do not have the facility to the same in our country. Malignant large cell calcifying Sertoli cell tumors, pituitary adenomas and melanotic schwannomas commonly occur in those with carneys complex and this needs to be kept in mind while on follow up.

Conclusion:

There is no specific conventional treatment plan for primary SCC of the orbit, which is relatively uncommon. From primary orbital radiation and observation to orbital exenteration with adjuvant chemotherapy and orbital radiation, we have studied a variety of research. In addition to surgical excision and chemotherapy, we used a multimodal approach to treat our patient that improve the survival status.

We hope that this instance draws attention to this incredibly rare disease, provides a glimmer of hope for those suffering from an otherwise fatal and progressing condition, and aids in the prevention of recurrence. Further research and awareness of this condition are crucial for improving patient outcomes and developing effective treatment strategies.

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Table 1: Literature Data Collection And Case study [4, 5, 7, 9, 13-16]

	Author	**Year**	**Age**	**Sex**	**Side**	**Site of lesion**	**Surgery**	**RT**	**Chemo**
[16]	Ruff et al	1985	53	F	Left	Inferotemporal orbit	Yes	Yes	No
[7]	Saha et al	2011	56	F	Right	Orbital apex	No	Yes	No
[5]	Peckinpaugh et al	2012	43	F	Right	Orbital apex	No	Yes	Yes
			63	M	Left				
			67	M	Right				
[15]	Hromas and Sokol	2014	43	M	Left	Inferior interconal space	Yes	Yes	No
[14]	Choi et al	2014	74	F	Left	Superomedial orbit	Yes	Yes	No
[13]	Arbulu et al	2017	73	F	Right	Superior orbit	Yes	Yes	No
[9]	Blandford et al	2018	63	M	Right	Superomedial orbit	Yes	Yes	Yes
[4]	El Samkary et al	2021	99	F	Left	Superolateral orbit	Yes	No	No
New	Rahman et al (Our case) **	2022	62	M	Right	Superolateral orbit	Yes	Yes	No

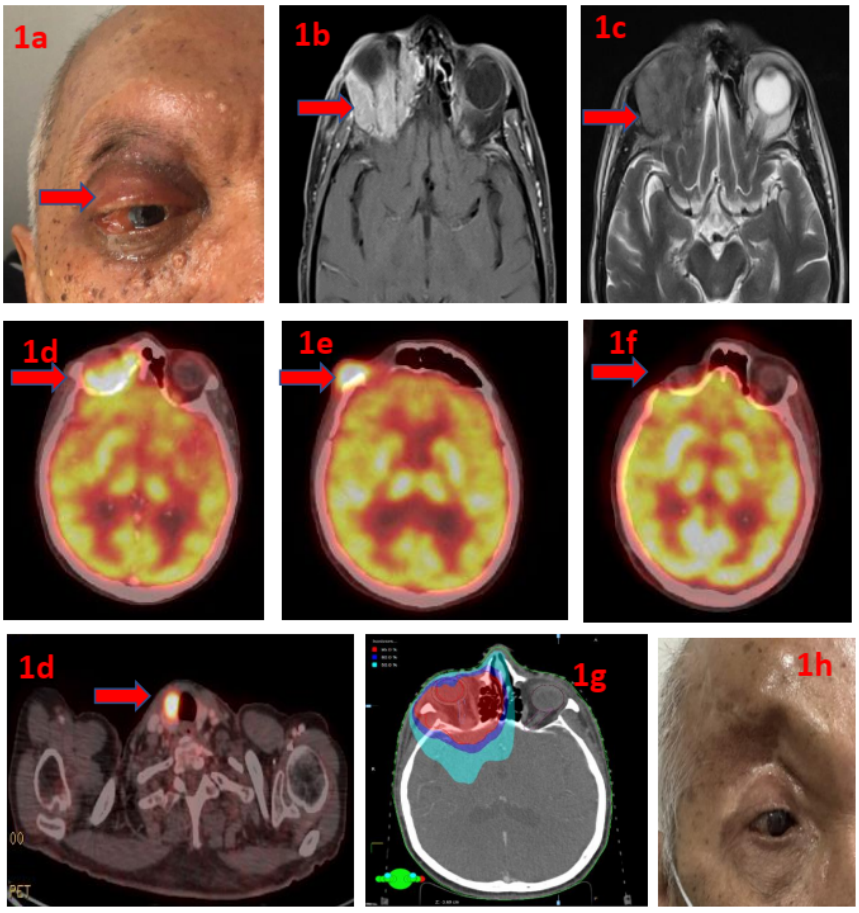

Figure 1

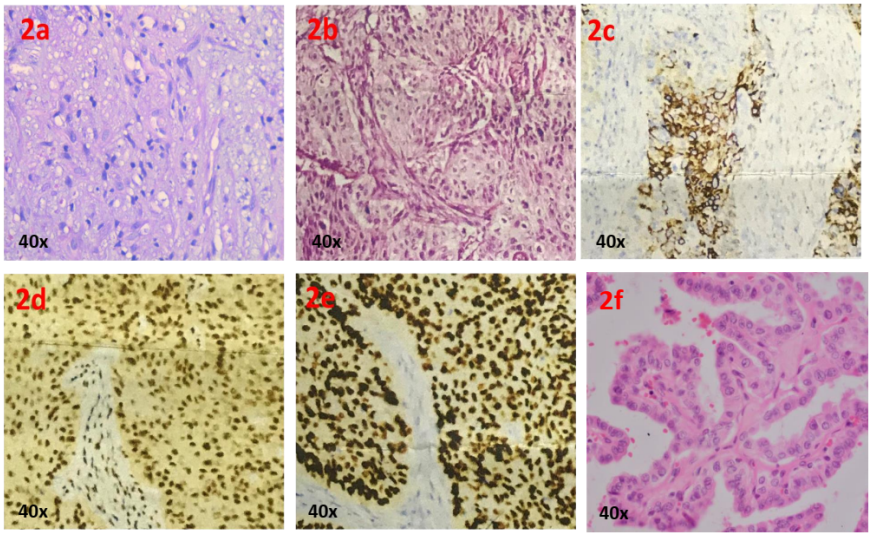

Figure 2

** - Ours is the first case of orbital tumor in a patient with carneys syndrome.

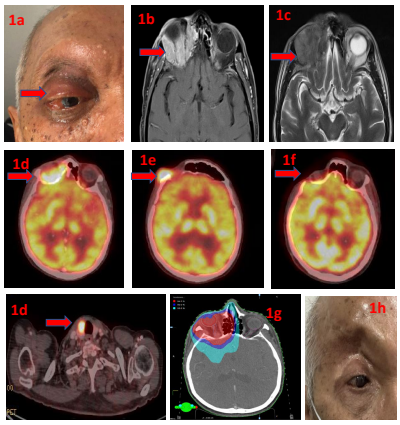

Figure-1 Legend:

- 1a- Patient photograph during treatment, Arrow showed edematous conjunctiva and swelling.
- 1b- MRI of Orbit Post excision biopsy (T1 Contrast), Arrow marked showed hyperintense soft tissue mass are involving the retro-orbital right side area with extension to medial and lateral aspect.
- 1c- MRI of Orbit Post excision biopsy (T2), Arrow marked area showing the hyointense area in the same extension.
- 1d- PET scan (Base line), Arrow marked area showing the FDG avid area in Primary Orbit Right side of orbit with FDG avid region in right lobe of thyroid.
- 1e- PET scan, After CCRT and Before Reconstructive Surgery, Arrow mark area showing high FDG avoid region of residual disease.
- 1f- PET scan, Follow up after 2.5 years of treatment, Arrow mark area showing no uptake of FDG in the primary right orbit.
- 1g- Rapid Arc dose color wash during Radiotherapy showing 95% in Red, 80% in Blue, 50% in turquoise color.
- 1h- Recent photograph during last follow up visit in July 2023, 3.3 years after treatment.

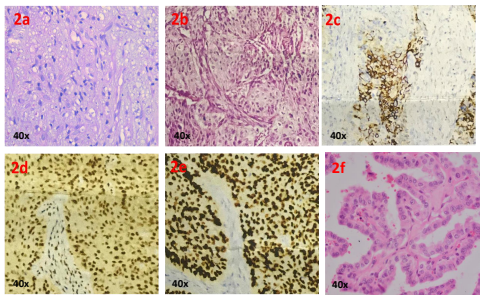

Figure Legend 2

- 2a- Myxoma ; H & E stain, low power image (x40) showing spindle shape cells in a myxoid background
- 2b- Orbital tissue-, H & E stain, low power image (x40) showing Squamous cell carcinoma, Grade- II
- 2c- Orbital Tissue, IHC of CK5/6 in low power image (x40) showing Tumor cell are Positive
- 2d- Orbital Tissue, IHC of p16 in low power image (x40) showing Tumor cell are Positive
- 2e- Orbital Tissue, IHC of p63 in low power image (x40) showing Tumor cell are Positive
- 2f- Total Thryoid specimen (Right lobe) H & E stain, low power image (x40) showing Papillary carcinoma Thyroid, Classic