



Case report

Choroidal metastasis as initial presentation of aggressive medullary thyroid carcinoma with widespread mediastinal, brain, pituitary, bone, lung, and liver metastasis: Case report and literature review

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ABSTRACT

Introduction: Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor that originates from the parafollicular C cells of the thyroid gland. MTC can be due to sporadic or hereditary causes due to gain of function germ line mutations in the RET proto-oncogene. MTC presenting as ocular symptoms due to choroidal mass is rare with bad prognosis.

Presentation of case: A 38-year-old Sudanese male presented to Hamad General Hospital, complaining of sudden painless decrease of vision of the right eye of 3 weeks duration. After investigations using imaging methods, the patient was discovered to have metastatic MTC that presented as choroidal mass and metastasized to his lung, bone, brain, pituitary, liver and mediastinum.

Discussion: In terms of investigations, serum levels of calcitonin have superior diagnostic accuracy. Our patient undertook diagnostic imaging including ultrasonography, fine needle aspiration and computerized tomography (CT) scan and/or MRI imaging. He undertook total thyroidectomy and left neck dissection followed by stereotactic radiosurgery for the right orbit and pituitary. He then received systemic anti-RET therapy (Selpercatinib). At 5 months follow up there was dramatic drop in CEA from 888 µg/L to 164 µg/L, and calcitonin from >585.2 pmol/L to 354 pmol/L.

Conclusion: Choroidal metastasis as initial presentation of MTC is extremely rare and challenging to diagnose. Surgeons need a high index of suspicion when ocular symptoms accompany a neck mass or thyroid-related symptoms. MTC has a progressive course with involvement of blood vessels and neck lymph nodes. Choroidal metastasis of MTC is challenging to manage.

1. Background

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor that originates from the thyroid parafollicular C cells that are responsible for secreting calcitonin that reduces blood calcium levels. MTC comprises 2–3% of all thyroid cancers and usually presents as a painless thyroid nodule [1]. MTC can be due to sporadic or hereditary causes [1]. The sporadic form is much more common comprising 70% of all MTCs, the remaining 30% are due to gain of function germ line mutations in the

RET proto-oncogene, inherited as autosomal dominant [1]. Sporadic MTC usually occurs between the fourth and sixth decades of life [2]. Calcitonin is a tumor marker for MTC, is quantified by immunoradiometric assays (IRMAs), and its level is proportional to the extent of the tumor burden [3].

MTC is a rare aggressive tumor, known to metastasize most commonly to lymph nodes, and in some rarer cases, to bones and lungs via lymphovascular spread [1]. Uncommon metastatic sites include the liver, adrenal gland, kidney, pancreas, and skin [4]. Central and lateral

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compartment lymph node metastases are present respectively in 14% and 11% of patients with T1 tumors and in 86% and 93% of patients with T4 tumors [5]. About 70% of MTC patients presenting with a palpable thyroid nodule have cervical metastases and 10% have distant metastases [6]. Multivariate analysis showed that significant independent prognostic factors were age and stage of disease at the time of diagnosis [7,8].

Generally, the choroid is a rare site of thyroid cancer metastases, described in patients where the thyroid cancer has already metastasized to the breast, lung, and prostate [9]. Overall, ophthalmic sites of metastasis are rare; however, hematogenous metastasis from systemic tumors occur more commonly to the uvea than to other ocular tissues, this difference in frequency is speculated to be the result of the significant blood supply to the choroid via the posterior ciliary arteries [10]. Visual changes resulting from choroidal metastasis are not typically the primary presenting symptom of thyroid cancer metastasis in general [11].

We report a patient who initially presented with right progressive decrease in peripheral vision that led to diagnosis of choroidal mass of the right eye, then found to have unilateral left MTC thyroid nodule, together with extensive metastasis to multiple sites. We report this case in line with the updated consensus-based surgical case report (SCARE) guidelines [12]. In addition, we undertook a literature review of published cases of MTC presenting with choroidal involvement.

2. Case presentation

A 38-year-old Sudanese male presented to the emergency department of our institution (Hamad General Hospital, largest tertiary facility in Doha, Qatar), complaining of sudden painless decrease of vision of the right eye of 3 weeks duration. He consulted a private ophthalmic doctor who informed him that he had retinal fluids and referred him to a private hospital where a retinal mass and enlarged neck lymph nodes were discovered. The patient denied any history of recent trauma or eye pain. He was referred to our institution for further management.

At the emergency department of our institution, initial evaluation showed that his past medical history was significant for left eye cataract extraction and intraocular lens implantation since 9 months. Past social, environmental, family and employment history were unremarkable. He did not smoke, never consumed alcohol and was not on long-term medications.

Upon physical examination, visual acuity was counting fingers 1 m in the right eye and 6/6 in the left eye. Unaided fundus (dilated) cup-to-disc ratio (CDR) of the right eye was 0.6, with healthy neuroretinal rim, but with parafoveal exudative retinal detachment. CDR of the left eye was 0.9, with normal macula, flat retina, and normal periphery. There were no other significant ophthalmic findings. On general examination, his vital signs were normal and the patient appeared well and oriented but had left-side neck lymph nodes (20 × 20 mm) that were mobile, non-tender, not attached to the skin or sternocleidomastoid, not fluctuant, and with no overlying skin changes. There was an enlarged left lobe of the thyroid gland. The rest of the physical examination was unremarkable. The patient was admitted to internal medicine for further investigations, and the thyroid surgical team and ophthalmology team were consulted. Retinal examination showed choroidal mass and retinal fluid (Fig. 1), most likely to be a metastatic choroidal lesion. Fig. 2 shows the timeline and sequence of events.

3. Investigations

3.1. Blood

We observed high calcitonin levels (>585.200 pmol/L), CEA (503.0 µg/L), ACTH (68.6 pg/mL), cortisol (639.0 nmol/L), and prolactin levels (682 mIU/L). TSH and T4 were normal. CBC, liver and kidney functions were unremarkable.



Fig. 1. Fundus examination showing choroidal mass and retinal fluid.

3.2. Ultrasound (US) of the neck

US of the left thyroid lobe appeared homogenous with well-defined heterogenous lobulated lesion noted in the mid to lower pole (42.4 × 20.8 × 26.2 mm), with internal vascularity (Fig. 3). Multiple suspicious looking enlarged lymph nodes were also noted in the left parajugular and supraclavicular regions, the largest measuring 38.5 × 19 mm with hypervascularity (Fig. 4).

3.3. Ultrasound-guided fine needle aspiration (FNA) of thyroid

FNA of the thyroid was positive for left thyroid nodule malignancy. The cytomorphologic features were suggestive of MTC.

3.4. CT scan of the neck

CT of the neck with contrast showed multiple lymph nodes in the left IV region with heterogenous postcontrast enhancement. The largest lymph node measured around 22 mm and displayed central cystic necrosis with irregular marginal enhancement. The enlarged lymph nodes were compressing the left internal jugular vein. Few small lymph nodes were also seen in VI region with central necrosis and marginal enhancement, and there was an ill-defined heterogeneously enhancing lesion with posterior capsular breach seen in the left thyroid lobe. Deviation with mild narrowing of the trachea was also observed.

3.5. CT of the lung

CT of the lungs showed multiple bilateral pulmonary nodules with variable sizes, the largest (13 × 10 mm) had focal cavitation at the superior segment of the right middle lobe. Other tiny/miliary nodules were noted (Fig. 5).

3.6. MRI of head and orbit with contrast

MRI showed choroidal lesion in the right eye (13 × 5 mm) suspicious of metastasis (Fig. 6A and B). The left eye was aphakic due to left cataract extraction. There was abnormal pituitary gland with partial cystic area in the left posteroinferior aspect of the sella and resultant displacement of the remainder of the gland (Fig. 7A and B). There was also a left parafalcine enhancing extra-axial lesion (10 × 4 mm) (Fig. 8A and B).

3.7. CT abdomen

Coronal reconstruction of abdomen CT (post contrast) showed multiple hyper-enhancing liver lesions of variable size mainly in the right lobe with early arterial enhancement, the largest in segment VII measuring 22 mm (Fig. 9).

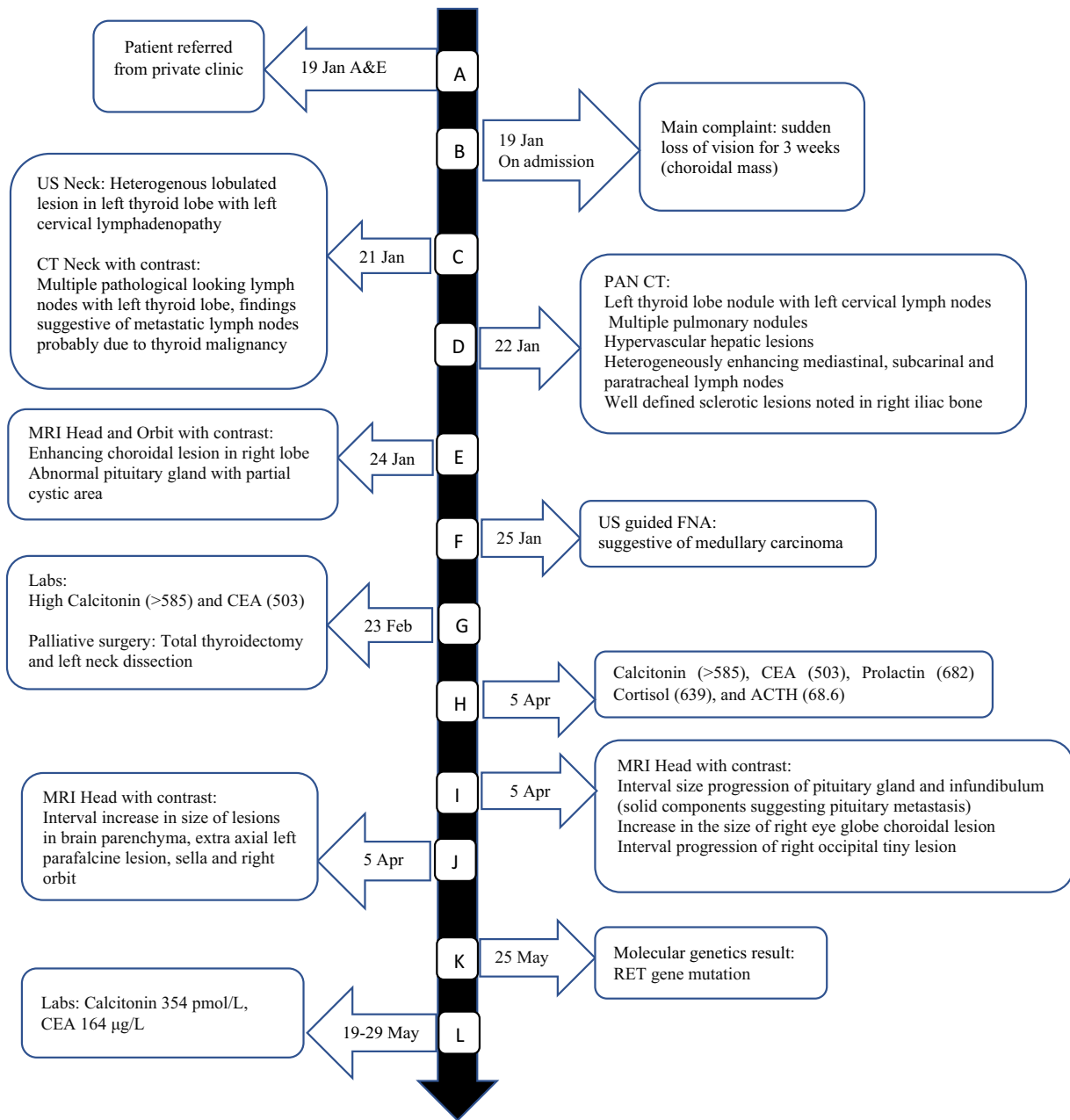


Fig. 2. Timeline and sequence of events during 2021.

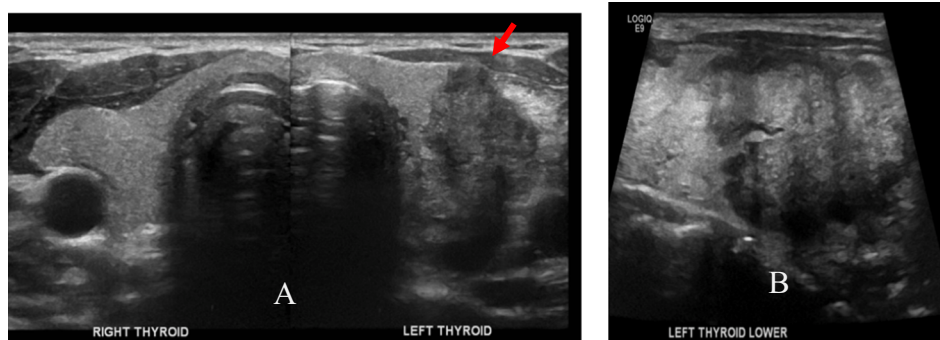


Fig. 3. Transverse (A) and sagittal (B) ultrasound views of thyroid gland showing lobulated heterogeneous hypoechoic solid nodule in left thyroid lobe.

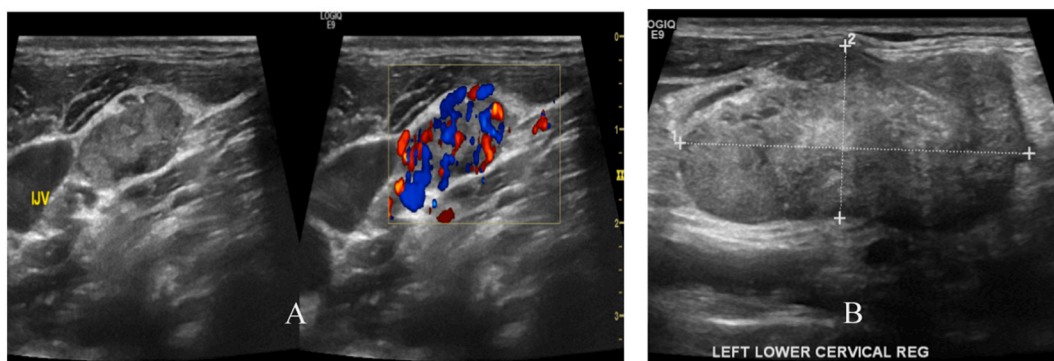


Fig. 4. Selected ultrasound transverse (A) and sagittal (B) views of neck showing multiple enlarged heterogenous hyper-vascular cervical lymph nodes.

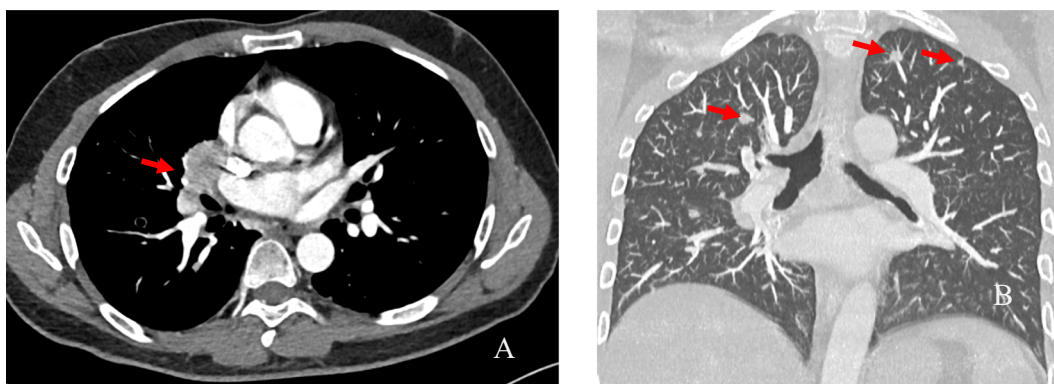


Fig. 5. (A) Axial chest CT post contrast showing enlarged heterogenous right hilar lymph node; (B) Coronal reconstruction of chest CT (lung window) showing multiple bilateral lung metastatic nodules.

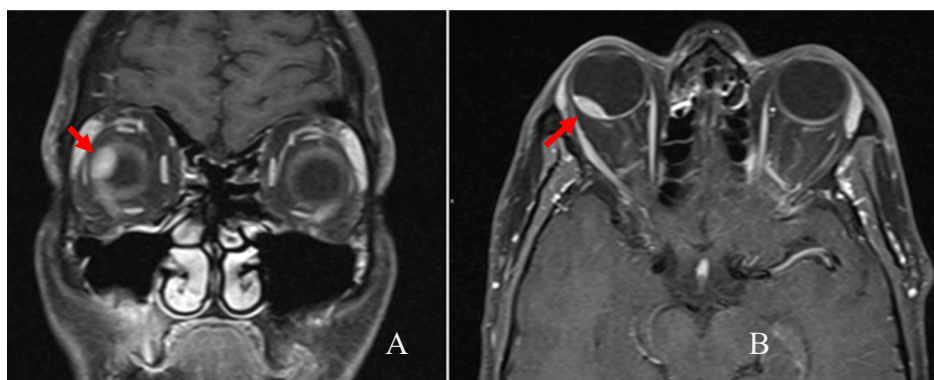


Fig. 6. Coronal (A) and axial (B) T1 post contrast MRI showing enhancing right choroidal mass.

4. Surgical technique and findings

The patient was discussed at our thyroid multidisciplinary team (MDT) meeting that recommended total thyroidectomy and neck dissection as palliative therapy. An experienced consultant thyroid surgeon undertook the procedure. After a collar incision extended on the left side at the level of anterior sternomastoid border, thyroid arteries and veins were ligated, recurrent laryngeal nerves were identified, parathyroid gland was preserved, and the thyroid was excised after shaving the tumor from the trachea. Left lateral neck dissection was undertaken, with dissection of the fascia over the sternomastoid muscle, internal jugular vein and carotid sheath. Excision of the lymph nodes at level 5 was undertaken. The intraoperative findings revealed a hard tumor of the left thyroid lobe adherent to the trachea and recurrent

laryngeal nerve with amalgamated multiple left side lymph nodes adherent to the lower part to the internal jugular vein, extending to the subclavicular region (Fig. 10).

5. Pathology

5.1. Final histopathology of thyroid

The histopathology of the left thyroid lobe showed MTC, and the right lobe showed benign thyroid cells with C-cell hyperplasia. Level V showed four lymph nodes positive for MTC. The size of largest metastatic deposit was 20 mm with extra-nodal extension. The cytomorphic features of the immunohistochemical staining were suggestive of MTC. Cell block preparation was attempted; however, there were not

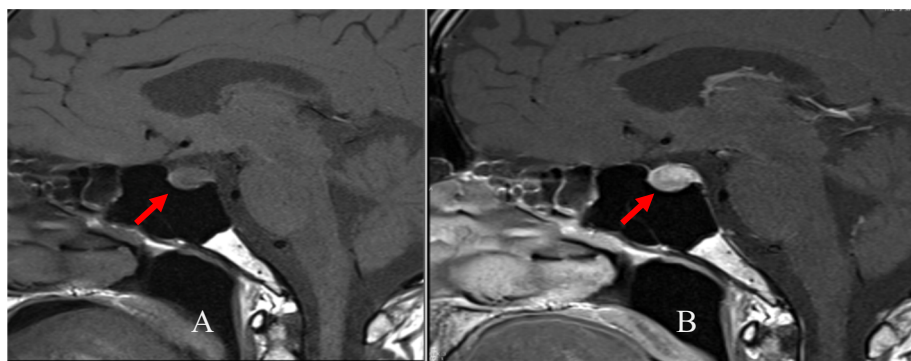


Fig. 7. Sagittal T1 pre (A) and post (B) contrast MRI brain showing enhancing seller mass involving the pituitary gland.

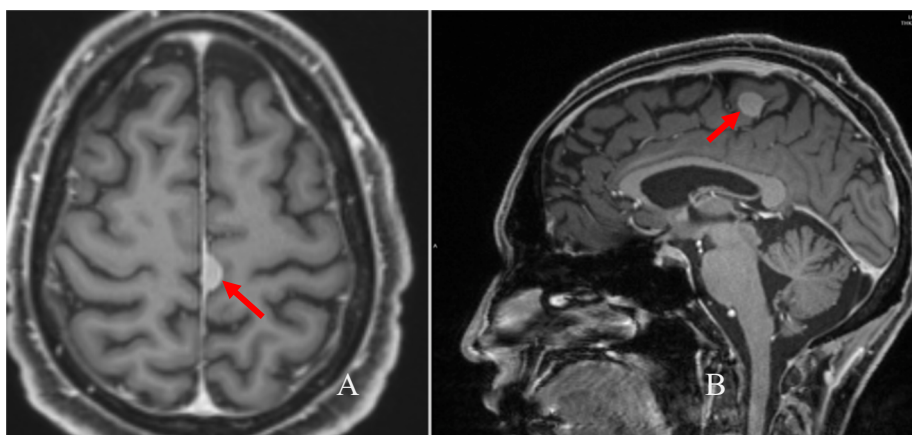


Fig. 8. Axial (A) and sagittal (B) T1 post contrast MRI brain showing enhancing left para-falcine mass.



Fig. 9. Coronal reconstruction of abdomen CT (post contrast) showing multiple hyper-enhancing liver lesions.

sufficient cells present to interpret the immunohistochemical stain results.

6. Follow up

The patient had no perioperative complications and was discharged after 2 days. The case was again discussed at the thyroid MDT meeting, and the decision was to refer the patient to neurosurgery for the brain lesions and to follow up at the thyroid oncology clinic.

Neurosurgery decided that no surgical intervention was required and recommended adjuvant therapy and the patient was referred to radiation oncology. The case was again discussed at the neuro-oncology MDT

meeting that recommended pituitary gland MRI with contrast. The MRI showed interval size progression of the pituitary gland, the pituitary infundibulum appeared more abnormal and bulkier than the previous scan with progression of the cystic and solid components suggesting pituitary metastasis, and the pituitary showed convex upper surface and thickened infundibulum indenting on the optic chiasma displacing it superiorly at the midline. There was also interval increase in the size of the: right choroidal lesion (measuring $\approx 22 \times 6$ mm vs 13×5 mm previously); right occipital tiny lesions (now measuring 4.6 and 3.6 mm); left parafalcine extra axial lesion (measuring 12×6 mm vs 9×4.7 mm previously).

The neuro-oncology MDT reviewed the new MRI results, and the decision was to start stereotactic radiosurgery for the multiple metastatic brain lesions, including the pituitary lesion. The patient undertook 5 sessions of cyberknife stereotactic radiosurgery (25 Gy in 5 fractions) on the right orbit and pituitary. Once the patient completed the stereotactic radiosurgery, he started systemic anti-RET therapy (Selpercatinib). The family was also scheduled for genetic counselling for MEN2A RET germline testing. Follow up five months later revealed a positive response to the systemic anti-RET therapy, with a dramatic drop in the tumor marker CEA from 888 $\mu\text{g/L}$ to 164 $\mu\text{g/L}$, and calcitonin from >585.2 pmol/L to 354 pmol/L. The patient was still continuing the systemic anti-RET therapy (Selpercatinib).

7. Discussion

MTC accounts for 5–8% of all malignant thyroid tumors [13]. Most cases occur sporadically with peak onset in the fifth and sixth decade of life [14]. In terms of demographics, research of 1252 MTC cases found that the majority (87%) were white, 60% were female [15]. As for

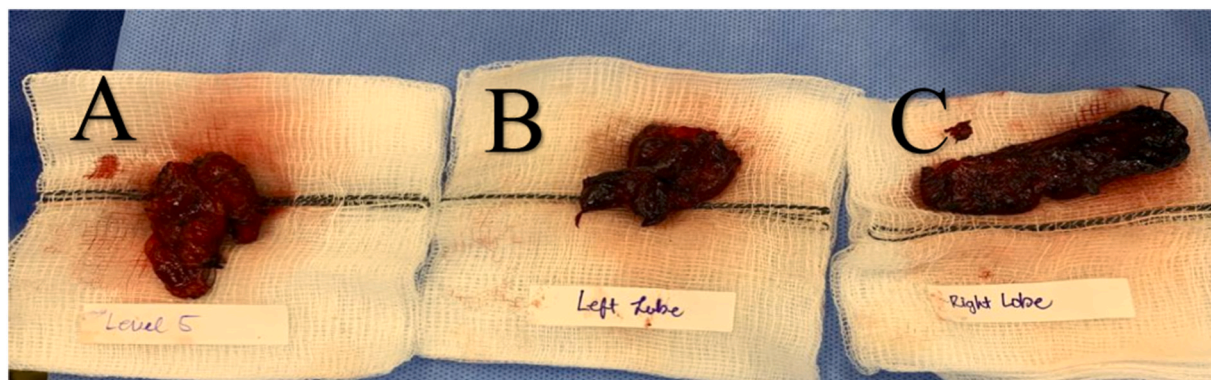


Fig. 10. Post thyroidectomy and lateral dissection specimens showing: (A) Amalgamated multiple left side lymph nodes; (B) Hard tumor of left thyroid lobe; and (C) Normal right lobe.

gender, our literature review [Table 1](#) shows that the cases identified exhibited a male predominance, again in support of the male sex of our patient. Our patient's age (38 years) supports the age range of the MTC cases presenting with choroidal involvement identified in the literature review we undertook (range: 23–63 years, [Table 1](#)).

In connection with the clinical presentation, [Table 1](#) shows that the current patient had the diagnosis of choroidal involvement before the diagnosis of MTC was established as the patient presented with decreased vision. In contrast, all the cases in the review had the diagnosis of choroidal involvement only after the diagnosis of MTC was established and thyroidectomy was undertaken, with an average of 11.5 years between the initial diagnosis with MTC and the diagnosis of choroidal metastasis manifesting as total vision loss [17], decreased vision [16,19,23], or conjunctivitis [20,21].

As for investigations, studies of MTC patients found that serum calcitonin had equal or superior diagnostic accuracy compared to procalcitonin [24,25]. However, a high procalcitonin to calcitonin ratio was correlated with an increased risk of progressive disease and shorter progression-free survival, useful in predicting prognosis [24,25]. These findings agree with the present case where the calcitonin level was significantly high. In addition, although we removed the primary tumor (total thyroidectomy), the calcitonin levels did not decrease, prompting further investigations that led to the diagnosis of metastatic MTC.

In terms of imaging, the definitive diagnosis for MTC is US-guided FNA followed by immunohistochemical staining to discriminate between MTC and other tumors [26]. [Table 1](#) shows that this is the procedure followed in all the cases we identified. In our case, the FNA histopathological results showed MTC. However, the ocular involvement of MTC may be a diagnostic challenge because many metastatic tumors are not detected using scintigraphy or radiologic imaging; therefore, clinical evaluation is important for the early diagnosis of ocular involvement [27]. After abrupt changes in visual acuity, fundoscopic examination with indirect ophthalmoscopy and ocular ultrasonography can identify and monitor choroidal metastatic deposits and are the mainstay of diagnosis [27,28]. Our investigations agree, as fundoscopy was sensitive and diagnosed the choroidal mass, and follow up using fundoscopy detected the significant interval increase in the choroidal mass.

As for metastasis, our patient did not show distinctive systemic symptoms (e.g., multi organ failure, in agreement with most cases in [Table 1](#)) [28]. For our case, the investigative techniques we used detected the primary tumor as well as the nodal, choroid, pulmonary and hepatic metastases.

In terms of management, metastatic MTC requires total thyroidectomy with uni or bilateral neck dissection when there is metastasis to the lymph nodes as in our case and all cases in [Table 1](#) (except two cases [11,19]). For ocular involvement, there is very limited data describing its treatment efficacy. Options include enucleation, photodynamic

therapy, external beam radiation therapy (EBRT), brachyradiotherapy using 125I episcleral radioactive plaque insertion, targeted monoclonal antibodies, and chemotherapy [27–31]. Enucleation is the treatment of choice for ocular metastases of thyroid carcinomas that cause definitive loss of vision and/or persistent pain [27]. However, our patient did not have a total loss of vision, hence the MDT decided that enucleation was not necessary.

Treatment of brain metastases by surgical resection, EBRT, or stereotactic radiosurgery may provide local control and improve the quality of life; however, patients usually succumb from progressive systemic disease within a short time after the diagnosis of central nervous system metastases [32,33]. [Table 1](#) shows that all the patients identified in our review did not have CNS metastasis (except our patient). In terms of brain lesions observed in our patient, the MDT and neurosurgeons did not plan surgical intervention and suggested adjuvant stereotactic radiosurgery for the multiple metastatic brain lesions, including the pituitary lesion taking in consideration the poor prognosis that the patient presented with and the distant metastasis to multiple organs. Hence the patient was referred to and undertook 5 sessions of cyberknife stereotactic radiosurgery (25 Gy in five fractions) on the right orbit and pituitary.

As for prognosis of metastatic MTC, there has been no significant trend toward an earlier stage of disease at the time of diagnosis, as others found that just under half of the patients presented with stage III or IV disease and there has been no significant increase in patient survival [15,34]. [Table 1](#) shows that all the cases of metastatic MTC (including the current case) showed an advanced stage 4 (T1b, N1b, M1). Distant metastases at diagnosis projects poor prognosis, with only 40% survival at 10 years [15]. Our literature review agrees, as [Table 1](#) shows that all the patients (except our patient) died within 9 months after choroidal metastasis was diagnosed. As metastatic MTC is incurable, the management aims to control loco-regional disease, hormonal excess (e.g., diarrhea or Cushing's syndrome), symptomatic metastases (e.g., pain or bone fracture), and metastases that threaten life (e.g., bronchial obstruction or spinal cord compression) [35]. Generally, the clinical usefulness of each treatment modality must be individualized based on the extent of the tumor, potential for improvement, risks of therapy, and patient preferences [36].

In terms of genetics, familial forms of MTC account for 25% of all MTC cases caused by gain-of-function germline mutations in the RET gene, and are inherited in an autosomal dominant fashion [14]. The genetic analysis (next generation sequencing) of our patient confirmed the presence of somatic RET mutation in axon 15, and out of the total 10 cases we identified, 7 had confirmed RET mutation. Once our patient completed the stereotactic radiosurgery for the right orbit and pituitary, he was started on systemic anti-RET therapy (Selpercatinib). The family was also scheduled for genetic counselling for MEN2A RET germline testing. Evidence suggests that the presence of a somatic RET mutation

Table 1

Literature review: cases of medullary thyroid carcinoma presenting with choroidal involvement.

Study	Age/ sex	Clinical presentation	Delay ^a	Ophthalmologic metastasis	Other metastasis	MEN- associated or sporadic	DX	Management	Patient status
Current case Qatar 2021	38/ M	R eye sudden vision impairment	Initial presentation	CM	Liver, lung, bone, pituitary, brain, mediastinal	MEN2B	CT, MRI, FNAB, US	TT, L neck dissection, SR	Alive
Gajdzis [16] France 2018	47/ M	Impaired vision (decrease acuity)	33 years	9 mm CM located in the P pole of L eye	Bone, parotid, lung, mediastinal LN	MEN2A	FNA, CT	TT, neck dissection	NR
Yildiz [17] Turkey 2011	63/ M	Sudden loss of vision in R eye	Couple of months	Optic disc and CM in R eye; small metastasis in P pole of L eye	Mediastinum, lungs, liver, bones	Sporadic	US, CT, MRI	TT, L. neck dissection, left supraclavicular LAP excision, R, C	Died 2 months after choroidal metastasis
Bianciotto [18] USA 2008	56 M	Enlarging mass of R upper eyelid.	36 years	2 amelanotic, CM in R eye, 3 similar tumors in L eye	Supraclavicular LN, pulmonary metastasis, hepatic	MEN 2B	US, F	TT, LN dissection, radiation	NR
Palm [19] Netherlands 2007	42/ M	Decrease visual acuity	10 months	Bilateral multiple yellow uveal masses	Mediastinal (paratracheal) lymph nodes, bones, lungs	Sporadic	F, US, LNB	BA, radiation to both eyes	Expired, exact duration NR
Søndergaard Pedersen [20] Denmark 2006	29/F	Keratoconjunctivitis sicca, bilateral corneal ulceration	NR	Five choroidal lesions in R eye; two in L eye	Skeletal, P, MH, intestinal abnormalities, increased joint laxity, prominent lips, multiple noduli on anterior tongue	MEN 2B	F, FA, US	NR	3 months (pneumonia)
Rosario [21] Portugal 2005	35/ M	Cervical and mediastinal nodes, bone metastases	8 years	Yellow CM, mild conjunctivitis	Bilateral cervical and mediastinal LN; lung, hepatic, vertebral, pulmonary	MEN 2B	US, F, CT, FNAB	TT, radiotherapy	6 months after diagnosis of CM
Shields [11] USA 2002	36/F	NR	16 years	Yellow CM	MN lip, tongue, prominent corneal nerves in both eyes	MEN 2B	NR	Radiation	9 months
Koh [22] Australia 1995	23/ M	MN lip, tongue, eyelids, MH, prominent corneal nerves	6 years	Post mortem examination (MTC in choriocapillaris)	Choriocapillaris, peritoneum, liver, lungs, kidneys, trachea, bone, prostate, myocardium	MEN 2B	US, CT, TBBS	TT	Expired, exact duration NR
Gysin [23] Germany 1979	47/F	Impaired vision (yellow placoid CM, surrounding retinal detachment)	4 years	CM L eye; 3 months later, multiple small metastases in R eye	NR	MEN 2B	NR	TT, cryo- and photocoagulation	7 months

Due to space limitations, only the first author is cited; BA: bilateral adrenalectomy; C: chemotherapy; CM: choroidal mass; CT: computed tomography; F: female, F: funduscopy; FA: fluorescein angiography; FNAB: fine-needle aspiration biopsy; L: left; LN: lymph node; LNB: lymph node biopsy; M: male; MEN: Multiple endocrine neoplasia; MH: Marfanoid habitus; MRI: magnetic resonance imaging; NR: not reported, P: posterior; Ph: pheochromocytoma; R: radiotherapy; R: right; RD: retinal detachment; SR: stereotactic radiosurgery (Cyberknife); TBBS: total body bone scan; TT: total thyroidectomy; US: ultrasonography.

^a Delay between eye symptoms and initial diagnosis.

correlates with a worse outcome of MTC patients, not only for the highest probability to have persistent disease, but also for a lower survival rate in long-term follow up [37]. Moreover, the presence of a somatic RET mutation correlates with the presence of lymph node metastases at diagnosis, which is a known bad prognostic factor for the definitive cure of MTC patients [37]. Notably, the RET mutation and the presence of lymph node metastases were positive in our case.

8. Conclusion

Choroidal metastasis of MTC is extremely rare and challenging to diagnose. Surgeons need to maintain a high index of suspicion when ocular symptoms accompany a neck mass or thyroid-related symptoms. Diagnosis of MTC based on the choroidal mass requires thorough investigations and should undergo FNA, CT, MRI, and lab tests. MTC has a slow and progressive course with involvement of blood vessels and neck

lymph nodes. Choroidal metastasis of MTC is also challenging to manage. The main objective of therapy is the radical ablation of the tumor masses via total thyroidectomy with bilateral central, mediastinal, and lateral neck dissection. Further research to investigate the role of radiation therapy in the palliation and local control of post-resection and advanced stage MTC are required. The decision to undertake palliative total thyroidectomy and neck dissection needs to be weighed side by side with any other potential interventions for the metastasis taking into account the staging, prognosis, and resultant quality of life. Hence for many cases of severe metastatic MTC, palliative therapy might remain the preferable choice. To the best of our knowledge, MTC presenting as ocular symptoms due to choroidal mass has not been previously reported.

Ethical approval

Approved by Medical Research Center, Hamad Medical Corporation reference number (MRC 04-21-692).

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CRediT authorship contribution statement

Mohamed S. Al Hassan: data collection, data interpretation, writing the paper. **Walid El Ansari:** study concept, data interpretation, writing the paper. **Ahmad Alater:** data collection, data interpretation, writing the paper. **Adham Darweesh:** Imaging, data interpretation, editing the paper. **Abdelrahman Abdelaal:** study concept, data interpretation, editing the paper. All authors read and approved the final version.

Guarantor

Prof Dr. Walid El Ansari: welansari9@gmail.com

Research of registration

Not first in Man

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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