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Tumor metastasize to thyroid, choroid: A rare manifestation

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Abstract

A 56-year-old male presented with flashes and floaters in his right eye. Fine needle aspiration (FNA) of right eye choroid and displayed metastatic carcinoid tumor. Computed tomography showed a 5cm right lower lung mass. Two years later, a mass was found in the thyroid left lobe with cervical lymphadenopathy. FNA of thyroid left lobe and mid-pole showed again neuroendocrine carcinoma. Everolimus and palliative radiotherapy was continued, and patient was enrolled on a clinical trial of temozolomide and bevacizumab. Carcinoid tumor metastases to the thyroid or eye (choroid) have been rarely reported. Early diagnosis and effective treatment with early palliative therapeutic program can be critical as the primary treatment.

Keywords

carcinoid tumor; oncology; metastasis; thyroid; choroid

Abbreviations

FNA: Fine needle aspiration; NETs: Pulmonary neuroendocrine tumours; US: Ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; TAP: photodynamic therapy; Lu-PRRT: peptide receptor radionuclide therapy

Introduction

Pulmonary neuroendocrine tumours (NETs) are categorized into typical and atypical carcinoids, large-cell neuroendocrine carcinomas, and small-cell carcinomas [1]. Typical carcinoid tumors are identified as well-differentiated tumors of neuroendocrine cells, with an overall 5-year survival rate of 70% [2]. Carcinoid tumors are primarily low-grade neoplasms stemming usually from neuroendocrine cells of the bronchial and gastrointestinal tracts. These tumors have neurosecretory granules and may be linked with neurosecretory syndromes. Clinical carcinoid tumors metastasize in 50–75% of patients, with common sites being lymph nodes, liver, and bone [3]. Carcinoid tumors can be linked with over-production of bioactive peptides such as serotonin, resulting in the carcinoid syndrome which is characterized by symptoms of diarrhea, flushing, hypotension, or bronchospasm. Carcinoid syndrome may be the first sign of an occult carcinoid tumor [2].

Carcinoid tumor metastases to the thyroid or eye (choroid) have been rarely reported [3]. About one-third of patients with choroidal metastases have no previous cancer history [2]. The incidence of ocular metastases in the United States is estimated to be 20,000 per annum [4]. Solid carcinoid tumor

metastases to the thyroid are barely reported during follow-up, despite the thyroid gland having rich blood supply. Lin et al. reported that 1.4% of 1,013 thyroid cancer patients had metastatic tumors, and that adenocarcinoma and squamous cell carcinoma were the most commonly found histology's [5].

Imaging techniques including computerized tomography (CT), magnetic resonance (MRI) imaging, and fluorescein angiography have been traditionally used to discover and categorize these lesions. However over the last decade, radiopharmaceutical-labeled imaging techniques are widely being used in localize carcinoid lesions [3]. This is a rare case of the carcinoid tumor metastasizing to the eye and thyroid. Less than 40 cases have been reported on this so far globally.

Case Presentation

A 56-year-old male presented to the ophthalmologist with flashes and floaters in his right eye for a few weeks. He denied blurry vision, photophobia, headache, or eye pain. Detailed work-up—including ophthalmoscope, fundus, and retinal examination—was performed. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) of the eye and brain suggested right eye choroid melanoma. However, fine needle aspiration (FNA) of right eye choroid suggested metastatic carcinoma instead of melanoma.

CT chest, abdomen, and pelvis, with positron emission tomography (PET) CT, showed a 5cm right lower lung mass. Right middle and lower lobectomy and biopsy results displayed metastatic carcinoid tumor. The patient received repeated intraocular plaque radiotherapy and photodynamic therapy (PDT) on multiple carcinoid tumor of the right eye, with constant observation and his vision was not affected. Two years later, he developed swelling in the neck. US of the neck showed a mass in the thyroid left lobe with cervical lymphadenopathy. FNA of thyroid left lobe and mid-pole showed neuroendocrine carcinoma consistent with metastasis from known carcinoid tumor. Figure 1 shows sonogram of left thyroid (Figure 1).

Reimaging of the entire body displayed multiple liver masses. FNA of the liver mass again showed low-grade neuroendocrine cancer. The patient denied any complaint of flushing, palpitations, diarrhea, etc. He was started on cisplatin and etoposide, which was well-tolerated. However, the disease continued to progress, as CT abdomen showed more liver masses (Figure 2). He was then started on everolimus oral daily. He then presented with right shoulder and right hip pain. Bone radiography showed multiple sclerotic lesion, and thus he received radiotherapy. Although his pain decreased, reimaging displayed more liver metastases and bone lesions, but thyroid mass was stable. Everolimus and palliative radiotherapy was continued, and patient was enrolled on a clinical trial of temozolomide and bevacizumab.

Discussion

Carcinoid tumors usually metastasize to the liver. If it is more than 2cm, the usual symptoms are flushing, palpitation, and diarrhea. Very rarely does it metastasize to the eye and thyroid. In fact, less than 30-40 cases have been reported so far in the entire world. In our patient, the carcinoid tumor not only metastasized to the liver and bone (later), but also it initially spread to rare locations including eye and thyroid. Our patient had no symptomatic manifestation of carcinoid syndrome.

Of all uveal metastases, 2.2% are from carcinoid tumors, whereas metastases to the orbit are

are considered more rare [3]. 88% of all uveal metastases consist of choroidal metastases and involve the post-equatorial part of the fundus [6-7]. Most choroidal metastases are asymptomatic unless there is direct connection with macula. Symptoms of choroidal metastases include blurred vision (80% of patients), pain (14%), photopsia (13%), red eye and floaters (7%), and field defects (3%) [7]. The differential diagnosis of choroidal metastases include choroidal melanoma, choroidal osteoma, choroidal hemangioma, choroidal neovascularization with disciform scarring, tuberculoma, and posterior scleritis[7]. In our patient, an ocular presentation (i.e., flashers and floaters) was the first clinical sign of metastatic carcinoid tumor.

Choroidal metastases can sometimes cause symptoms resulting in primary diagnosis of other tumors such as lung cancer, breast cancer, and melanoma. However, most patients have late symptoms of the disease [8].

Carcinoid tumor metastases to the thyroid are reported to be very rare, as most patients in one study were found to die within nine months after diagnosis. Aggressive tumors cause painful thyroid nodules with quick development and localized compression symptoms. The slow growth of well-differentiated neuroendocrine tumors (atypical carcinoid) may be the cause for the lack of thyroid destruction and local symptoms. In cystology or on histopathology, metastatic thyroid lesions from neuroendocrine tumors can be like medullary thyroid carcinoma on cytology or on histopathology [9].

The diagnosis of ocular metastases is mainly based on clinical findings, which can include imaging studies and histopathology. Choroidal metastases are usually pale yellow in color expect with thyroid, renal cell, and carcinoid metastases, which are orange. Choroidal metastases are commonly linked with substantial subretinal fluid and a retinal detachment. However, this patient did not show a detachment [6].

Diagnosis of thyroid metastases includes considering the possibility of metastasis in patients with thyroid nodules and a history of a primary malignant tumor [9]. Ultrasound (US) guided fine-needle cytology (FNB) are more advanced diagnostic tools for papillary thyroid cancer (PTC) [10]. Although PTC prognosis is favorable with low10-year mortality rate and a long-term survival rate, 20% of patients are reported to have loco regional recurrences and PTC-related deaths. Especially in older patients, lymphatic metastases may affect recurrence and survival rates. The main risk factors for PTC recurrence include multifocal primary tumor, infiltration of thyroid capsule, patient age (young or old age), tumor size, several oncogenes (p53, BRAF), are linked with node involvement. Patients are high risk of loco regional include males aged 45 years or more, with aggressive histotypes, capsular or loco regional infiltration, incomplete tumor resection, and BRAF positivity [10]. Anaplastic carcinoma (ATC) belongs to a group of killer tumors with extremely low life expectancy/prognosis because of its rarity, aggressiveness, and quick metastasization [10,11]. The most common thyroid neoplasms are papillary variants, with follicular and medullary cancers (part of the MEN-2 syndrome) [10].

Thyroid nodules found during follow-up of patients with neuroendocrine tumors must be extensively examined. Thyroid fine-needle aspiration biopsy usually confirms the diagnosis, resulting in correct management without unnecessary treatment approaches [9]. In our patient, FNA of thyroid left lobe and mid-pole showed neuroendocrine carcinoma consistent with metastasis from known carcinoid tumor (Fig. 1).

Another diagnostic test for thyroid metastases is detection of thyroid transcription factor-1 (TTF-1)—a nuclear homeodomain transcription factor which is specifically expressed in developing respiratory epithelium, thyroid and diencephalon—is critical since immunohistochemical studies have shown that TTF-1 is expressed in certain types of lung and thyroid neoplasms, including pulmonary neuroendocrine tumors and medullary carcinoma of the thyroid [12]. TTF-1 is positively expressed in 70–95% pulmonary well-differentiated neuroendocrine tumors (typical carcinoids) [12]. Thus, TTF-1 staining is now regularly used to differentiate metastases from a primary lung carcinoma, and from metastases of non pulmonary carcinomas [12].

The primary systemic cancer is never found in some cases, and thus a tissue diagnosis is needed [4]. The histological diagnosis of these tumors are determined using typical immunohistochemistry. Immunohistochemical markers such as chromogranin A, neuron-specific enolase and synaptophysin are positive for medullary thyroid and metastatic neuroendocrine carcinoma [12-13]. Calcitonin and carcinoembryonic antigen (CEA) immunohistochemistry is negative in metastatic neuroendocrine tumors [9]. However, in medullary thyroid cancer, positive staining is used to find increased serum calcitonin levels [5,9]. In our patient, serum calcitonin concentrations was normal with the histopathological and immunohistochemical findings of thyroid metastases [9].

Radiological diagnosis of pulmonary NETs depends on if the tumor is located centrally or peripherally, and multidetector tomography is usually suggested for both types. Bronchoscopy with biopsies can also be done for central tumors. Whole-body nuclear medicine imaging has an important role in detecting distant metastases. Since almost 80 % of lung NETs express somatostatin receptors (usually subtype 2), somatostatin receptor scintigraphy is useful is diagnosing well-differentiated lung tumors. Furthermore, diagnostic 18F-FDG PET can be positive if the disease is aggressive [1].

Treatment of metastatic carcinoid tumours includes palliative surgical removal and chemotherapy with or without a-interferon and hepatic artery embolization—all of which do not completely control the tumor. Several studies on the response to treatment with cytotoxic chemotherapeutic agents found an objective response of 20–30% with a median overall survival of 24.3 months. For limited disease, radical surgery is preferred for having the best long-term prognostic factor [1]. However in most cases, the main therapy is symptomatic control with antidiarrhoeal agents and somatostatin analogues. New agents such as temozolomide enhance clinical benefit compared to classic standard treatments of chemotherapy and radiotherapy [1].

Third-line alternatives or additions to chemotherapy and radiotherapy include peptide receptor radionuclide therapy (Lu-PRRT)—a small peptide linked with a radionuclide releasing beta radiation to systemically treat metastasized neuroendocrine tumors—and 131I-mIBG therapy, which is analogous in phaeochromocytomas, paragangliomas and carcinoid tumours, and radiotherapy in patients with uptake on diagnostic 123I-mIBG [1,13]. Previous studies on 131I-mIBG therapy showed that most patients had a halt in tumor progression, more than 50% lower hormonal levels, and 75% of patients with symptomatic responses and better quality of life. 131I-mIBG therapy is known to be safe, well-tolerated, with low acute and long-term side-effects [13]. Although a few studies suggested that 131I-mIBG therapy plays a role in carcinoid tumors, the usefulness of this therapy for this tumor needs further detailed analysis [1].

Ocular metastases may react to chemotherapy, but can take several months to change in

appearance [6-7]. Instead, radiotherapy is more commonly used for these tumors. This is usually from an external source, such as X-rays, with or without lens-sparing methods. If the retinal pigment epithelial function is still undamaged, subretinal fluid resolves by restoring visual acuity. External beam radiotherapy was found to be successful restoring vision in approximately 86% of patients. Proton beam radiotherapy and external radiotherapy have also been used, but they are either expensive or time-consuming [4]. On the contrary, internal plaque brachytherapy with iodine or ruthenium can be effective for small solitary choroidal metastases, as it can be done in a few days and is especially useful in patients with lower life expectancy [4].

Photodynamic therapy has also been successful in choroidal metastasis from carcinoid tumor when chemotherapy and radiotherapy did not work. Treatment is done using the standard photodynamic therapy (TAP) protocol (600mW/cm2 over 83 s) with intravenous verteporfin infusion. Subretinal fluid resolution and return of visual acquity occurs quickly over 6–8 weeks. However, the long-term benefit of this treatment is unknown[4]. Our patient received repeated intraocular plaque radiotherapy and photodynamic therapy (PDT) on multiple carcinoid tumor of the right eye.

Recently, intravitreal anti-vascular endothelial growth factor VEGF has been effective in treating choroidal metastases, especially for small, circumscribed uveal metastases without an exudative retinal detachment. The injections are repeated 4–6 times weekly. Both anti-VEGF and PDT treatments are preferred for patients who cannot withstand several daily hospital visits [4].

For thyroid metastases, peptide receptor radionuclide therapy with $_{177}$Lu-DOTATATE (Lu-PRRT) with chemotherapy provides positive outcomes [1]. In addition, somatostatin analogs have been used to treat ectopic adrenocorticotropic hormone secretion with varied success rates. For long-term treatment, antiproliferative and antisecretory effects of octreotide treatment for endocrine tumors may separate, causing sustained antiproliferative but decreased antisecretory effects [9]. Our patient was started on cisplatin and etoposide, which was well-tolerated. Overall, new diagnostic and therapeutic methods are needed for recurrent disease.

Considering the multifocal nature of PTC neoplasm, management includes effectiveness of radioactive iodine (RAI) treatment with follow-up of thyroglobulin (Tg) serum levels, and total thyroidectomy (TT) and thyroid stimulating hormone (TSH) suppression therapy [10]. For cases of limited disease, total thyroidectomy is recommended [11]. The role of lymph node dissection (LD) in ATC for recurrence and survival remains controversial [10,11]. Patients at high risk with advanced primary tumors require routine central lymph node dissection (RCLD) [10]. For PTC without suspicious enlarged lymph node, RCLD and lateral prophylactic node dissection are not indicated. RCLD is recommended in selected high risk cases. Low risk patients require a similar lymph nodal recurrence rate after TT without LD, lowering sickness [10].

To treat ATC patients, surgery is the first-line treatment to lower tumor burden and alleviate the least compressive complications. For patients unsuitable for radical surgery during clinical presentation (about 33% of patients), a subtotal resection with palliative intent is done [11]. Surgery, followed by chemo-radiotherapy, can greatly increase survival rate for early-stage ATC patients, although early-stage is very rare. Advanced disease is linked with poor prognosis and an overall survival of about 3-6 months [11]. Agents such as sorafenib, axitinib, imatinib and combretastatin A4 provided positive results in many

clinical trials. ATC is deemed a radioresistant tumor [11].

Treatment approach for locally-advanced ATC requires surgery, chemotherapy and radiotherapy to improved survival, especially in patients with 5 cm or smaller tumor size [10]. In addition, either radiotherapy, chemotherapy or both are suggested to improve loco-regional regulation and metastatic development [11]. Radiotherapy is known to control local invasion by prolonging local recurrence and hindering thoracic blockage. Hyperfractionated local radiotherapy, although higher in toxicity, proved to be more effective than traditional treatment [11].Radiotherapy combined with doxorubicin (10 mg/m2) might offer better results. Patients not suitable for surgery may have both chemo/radiotherapy. Previous studies show patients with 89% of local complete response rate with R0/R1 resection with chemoradiation, compared to 3% in patients without radiation and R0/R1 resection. Complete local response causes increased median survival and 1-year overall survival [11]. Nevertheless, ATC prognosis remains low and new treatment strategies are needed to fight this aggressive tumor. New drugs that target BRAF, angiogenesis, c-MET and EGFR may offer a possible option for unresectable patients [11].

Conclusion

In summary, metastases to the thyroid and eye are exceedingly rare with carcinoid tumors. Primary treatment to avoid visual deterioration includes early diagnosis and effective treatment with early palliative therapeutic program. Radiopharmaceutical imaging is an excellent tool to reveal distributed disease, find lesions, determine staging of the disease, and potentially improve quality of life with early diagnosis and treatment. Our patient was continued on everolimus and palliative radiotherapy, and enrolled a clinical trial of temozolomide and bevacizumab.

Figures

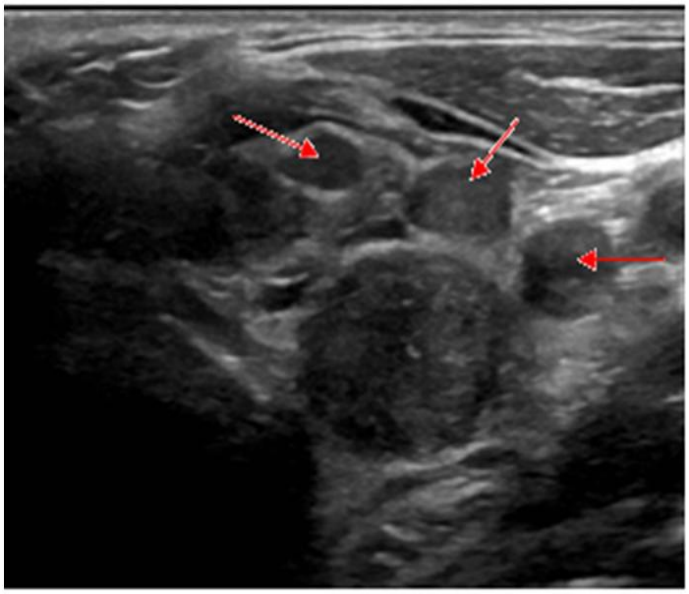

Figure 1: sonogram of left thyroid (Red arrows show multiple thyroid nodules).

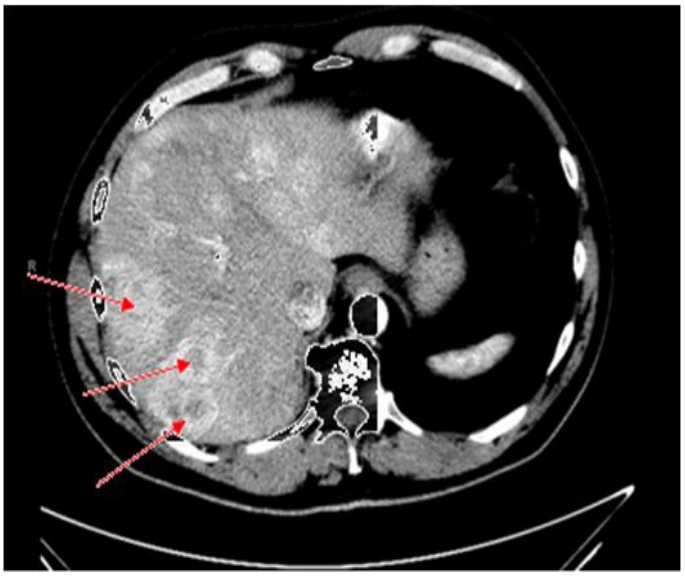

Figure 2: CT Abdomen / Pelvis with Contrast (Red arrows show multiple hepatic metastatic lesions).

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