Unusual presentations of differentiated thyroid cancer: analysis of 55 cases from North India

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Cancer of the thyroid is the most common endocrine malignancy. Most patients with well-differentiated thyroid carcinoma present with an asymptomatic thyroid nodule with or without regional lymphadenopathy or rarely with distant metastasis at diagnosis. Western series report a prevalence rate of 4% for metastasis outside the neck, but in an endemic iodine deficiency area like ours the overall prevalence of distant metastasis was 20%. In 17% of cases, metastases were detected synchronously and at multiple sites. Metastatic disease as the presenting manifestation is exceedingly rare. Patients with metastatic disease are usually asymptomatic and rarely present with organ-specific symptoms. We describe 4 patients with peculiar presentations.

Patients and Methods
Fifty-five consecutive patients, 15 male (27%) and 40 female (73%) with differentiated thyroid carcinoma, who had more than two follow-up visits in the Thyroid Clinic at Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh, over the last 10 years were included in this study. Their mean (±SD) duration of follow-up was 4.0±3.6 years ranging from 0.25 to 10 years. Their age ranged between 13-70 years with mean (±SD) age of 39.5±13.3 years. Twenty-nine (53%) patients had multinodular goitre, 24 (44%) had a solitary thyroid nodule and one had a diffuse goitre; another had no obvious thyroid swelling clinically. All were euthyroid at diagnosis except for 5 patients (9%), 4 of whom were thyrotoxic and one hypothyroid. Total thyroidectomy was done in 46 patients (84%), hemithyroidectomy in 8 (15%) and in 1 (2%) surgery was not done due to refusal. Analysis of histopathological data revealed that 35 (64%) patients had papillary, 5 (9%) had follicular variant of papillary thyroid carcinoma and 15 (27%) had follicular carcinoma. All patients except one, after total thyroidectomy, received an ablative dose of $^{131}$I and were on suppressive doses of L-thyroxine. Four patients (7%) had post-operative permanent hypoparathyroidism. We describe 4 peculiar cases out of 55 who had unusual presenting manifestations of the thyroid cancer (Table 1).

Case 1
A 30-year-old-man from an iodine sufficient area was admitted with sudden onset of flaccid quadriaparesis. He had no previous history or family history of similar episodes. However, he had a history of loss of 10 kg weight in 4 months with increased appetite, hyperdefecation, palpitation and tremulousness. On examination, his body mass index (BMI) was 20.3 kg/m² and had pulse rate of 112/min, and BP...
of 110/60 mm Hg. He had fine tremors, Plummer’s nail and a soft, diffuse grade II goiter with a firm, lymphadenopathy. His muscle bulk was decreased with a power of \( \frac{2}{5} \) in the lower limbs and \( \frac{3}{5} \) in the upper limbs, and deep tendon reflexes were diminished. Sensory examination was normal and there was no cranial nerve deficit. He had no thyroid associated ophthalmopathy or dermopathy. Other systemic examinations were normal. Laboratory studies at admission showed serum Na\(^+\) 140 mEq/L, K\(^+\) 2.4 mEq/L, Cl\(^-\) 109 mEq/L, HCO\(_3\)\(^-\) 26 mEq/L, Mg\(^{2+}\) 2.5 mEq/L, phosphate 3.8 mg/dL, T3 3.19 ng/mL (normal, 0.8-2.1), T4 253 ng/mL (normal, 40-120) and TSH was 0.05 µU/mL (normal, 0.3-6.0). Single random urine electrolytes were Na\(^+\) 78 mEq/L, K\(^+\) 28 mEq/L, Cl 95 mEq/L. Radioactive iodine uptake at 24 hours was 35% (normal, 15-35%) and whole body \(^{131}\)I scan revealed increased tracer uptake in the thyroid, lymph nodes and L5 vertebrae. Thyroid microsomal antibody (TMA) titres were insignificant. He was managed with parenteral potassium supplementation following which the patient’s muscle power improved to normal within 8 hours. He was put on neomercazole and propranolol and after achieving euthyroidism. Total thyroidectomy with lymph node resection was performed. Histopathology confirmed follicular thyroid carcinoma with lymph node metastasis. He received an ablative dose of \(^{131}\)I and is on L-thyroxine suppressive therapy. There was no recurrence of such episode on follow-up in the last 2 years.

**Case 2**

A 55-year-old woman, resident of an iodine sufficient area, had diffuse goiter for the past 25 years. She presented with rapidly increasing swelling in the right frontal region along with an increase in size of the goiter for the last 4 years. On examination, her BMI was 20 kg/m\(^2\), she had a pulse rate of 80/min, and no tremors. She had diffuse, firm and globular goiter (grade IV) with multiple tattoo marks and did not have cervical lymphadenopathy. The swelling in the right frontal region (6×8×6 cm) was globular, firm and pulsatile (Figure 1a) and she had another firm, pulsatile swelling in the left shoulder region. On investigation, thyroid function tests and serum biochemistry were unremarkable. An x-ray skull lateral view showed destruction of the frontal bone with adjacent soft tissue mass. CT scan head showed a solitary calvarial metastasis destroying the frontal bone with intracranial as well as extracranial extension into the adjacent soft tissue. \(^{131}\)I whole body scan

| Patient | Age | Sex | Cause of referral                      | Functional status | Histopathology |
|---------|-----|-----|----------------------------------------|-------------------|----------------|
| 1       | 30  | M   | Hypokalemic paralysis                  | Toxic             | Follicular     |
| 2       | 55  | F   | Pulsatile scalp swelling               | Euthyroid         | Follicular     |
| 3       | 70  | M   | Metastasis to globe                    | Euthyroid         | Papillary      |
| 4       | 47  | F   | Solitary thyroid nodule, ovarian mass   | Euthyroid after total thyroidectomy | Struma ovarii with follicular Ca |

Figure 1a. Pulsating metastasis on the right side of the frontal area with prominent blood vessels.

Figure 1b. \(^{131}\)I whole body scan showing significantly increased tracer uptake in the thyroid region and the skull.
showed significant increased tracer uptake in the thyroid region and skull (Figure 1b). 99mTc-MDP bone scan showed photopenic areas in the skull, left shoulder, multiple vertebrae and the seventh rib. She underwent total thyroidectomy uneventfully and histopathology confirmed follicular carcinoma and FNAC from osseous lesions showed metastases. She was subjected to 131I ablation for skeletal metastases followed by L-thyroxine suppressive therapy.

**Case 3**
A 70-year-old man from an iodine sufficient area presented with progressive loss of vision in the left eye of one-year duration and pain on movement of the globe. He was not a known diabetic, nor had any history of thyroid disease or ocular trauma. On examination, he was sick looking with a BMI of 27 kg/m². His vitals were stable and he was clinically euthyroid. Ocular examination revealed loss of light reflex, dilated pupil and choroidal mass in the left eye and a normal right eye. There was no visible or palpable neck swelling or lymph nodes anywhere else. For the painful blind eye due to intractable glaucoma he underwent enucleation. The histopathology of the excised tissue revealed metastatic papillary thyroid carcinoma involving the posterior choroid and superficial retina (Figure 2a, 2b). Anterior segment and optic nerves were uninvolved, while the retina was detached posteriorly. Immunostaining for thyroglobulin was positive in the tumor tissue. Color Doppler ultrasound of the neck done subsequently revealed neovascularization and 15×15 mm nodule in the right lower pole of the thyroid and a 2×2 cm lymph node near the common carotid artery. Fine needle aspiration cytology from the thyroid swelling and lymph node revealed papillary thyroid carcinoma (Figure 2c). He underwent total thyroidectomy and radical node resection followed by an ablative dose of 131I. Whole body 131I scan done subsequently found no residual disease. He was on a suppressive dose of L-thyroxine and doing well for the last 3 years.

**Case 4**
A 47-year-old woman from an iodine sufficient area presented with an euthyroid solitary nodule. It had poor 131I-uptake on scan and had features of follicular neoplasm on FNAC. Her thyroid profile was normal. She was planned for hemithyroidectomy but underwent total thyroidectomy for hemorrhage into the nodule on exploration. The detailed histology of the nodule excluded malignancy. She received 150 µg L-thyroxine daily for 3 years. However, even without thyroid hormone replacement she later remained euthyroid and had no palpable goiter and had normal serum T3 and T4 levels. Six years later, she complained of irregular cycles and experienced hot flashes and after screening was put on hormone replacement therapy (HRT) with conjugated equine estrogen and medroxyprogesterone continuously. With this therapy, hot flashes decreased but after 6 months she had inter-menstrual bleeding. A tender right fornix and 5×6 cm firm mobile mass was found on per vaginal examination and it was confirmed by pelvic ultrasound. Bilateral salpingo-oophorectomy and hysterectomy were performed. Histopathology revealed follicular carcinoma in a struma ovarii (Figure 3). No other teratomatous elements were seen. The left ovary was normal. Estrogen and progestosterone receptor status by peroxidase anti-peroxidase immunochemistry on ovarian tissue after microwave retrieval were found to be negative. An 131I whole body scan after 6 weeks of laparotomy revealed uniform low uptake in residual thyroid tissue (2.4% at 24 h) and no tracer uptake elsewhere. Her
Discussion

Most patients with thyroid cancer are euthyroid and thyroid cancer manifesting with thyrotoxicosis is rare. 6-9 Leiter et al described the first patient with adenocarcinoma of the thyroid with functioning metastasis and postoperative thyrotoxicosis in 1946. 6 Since then a handful of cases (less than 50) are described. Four out of 55 patients in our study were toxic at presentation, three had pre-existing MNG and one had a functioning metastasis and presented with periodic paralysis. The different mechanisms by which thyroid malignancy causes thyrotoxicosis include excessive production of thyroid hormones by functioning thyroid and/or metastatic tissue, excessive release of thyroid hormones by infiltration of the thyroid gland by the tumor tissue, underlying Graves’ disease, and iodine-induced toxicosis as a part of diagnostic or therapeutic interventions. 6-9 The association between thyrotoxicosis and periodic paralysis was initially described by Rosenfeld in 1902. 10 The prevalence being 8% to 34% in oriental males and 0.2% in females, while in non-Asian population the reported prevalence is 0.1% to 0.2%. 11-13 Thyrotoxicosis usually precedes or occurs concurrently with periodic paralysis in 80% of cases, like ours. 14 The disorder is clinically indistinguishable from familial hypokalemic periodic paralysis. The pathogenesis of periodic paralysis in thyrotoxicosis includes an alteration in either Na+/K+ ATPase pump activity due to thyrotoxicosis or increased 2 adrenergic receptor sensitivity. Increased insulin sensitivity and altered voltage gated calcium channels are also postulated. 15 Follicular thyroid carcinoma with thyrotoxic periodic paralysis as a presenting manifestation has not been reported previously.

Differentiated thyroid cancer commonly metastasizes to lymph nodes, bones, lung, brain and other organs. Osseous metastasis occurs in 3% to 12% of patients with differentiated follicular and papillary thyroid cancer. 12 However, 131 I scan or 99mTc-MDP scan can reveal osseous metastasis in the majority (74%) of these patients. 14 Of the two, relatively higher prevalence of bone metastasis occurs in follicular (15.2%) than in papillary carcinoma (0.6%). 16 Frequent sites of osseous metastases are sternum, vertebrae, pelvis and ribs. Case 2 presented with a pulsating metastatic deposit in the frontal bone, which though classical, is very rare as the presenting manifestation. The overlying skin was also involved as follicular carcinoma has a greater preponderance than papillary carcinoma for cutaneous metastases and the majority of skin metastases from thyroid cancer are localized to the head and neck area with underlying bone involvement. 17 However, one such case has been described in which the sacrum was the site of pulsating metastases. 18,19

Although secondaries are the commonest malignancy of the choroid, their occurrence is quite rare. In a study of 8712 patients with carcinoma, only 6 had metastasis to the choroid. 20 The reasons for rarity of choroid metastasis are early diagnosis of cancer and right angle branching of the ophthalmic artery, and therefore malignant emboli lodge into the brain and meninges by means of a straight route. 21 The other explanation in patients with disseminated malignancy could be the clinical picture dominated by a poor general condition, slow growth of choroid metastasis and death of the patient before attention is attracted to the ocular condition. Routine ophthalmic or pathological examinations of the eye are usually omitted in patients with terminal carcinomatosis. 20 The majority of emboli travel to the 20-old short posterior ciliary arteries rather than the long anterior branches. Therefore the posterior region of the choroid near the macula is the site of predilection.

The commonest malignancies metastasizing to the choroid are malignancy of the breast, lungs, colorectal region and urinary bladder. 20 Choroid metastasis of thyroid carcinoma is rare. Of 227 cases of choroid metastasis only one was from thyroid. 22 A review of the literature shows 14 reported thyroid cancers metastasizing to the eye; papillary thyroid carcinoma has been reported thrice before. 22-24 Patients with choroid metastasis may present with progressive loss of vision,
limitation of ocular movement and retro-orbital/orbital pain, though the majority are asymptomatic. Ocular examination usually reveals neovascularization of the iris, raised intraocular pressure, and exudative retinal detachment with an orange-colored nodule. B-mode ultrasound, MRI and biopsy in an appropriate setting clinch the diagnosis. The treatment modalities are \(^{113m}I\) ablation, photocoagulation, cryopexy and rarely enucleation.\(^{24}\) Our case is unique because the choroidal metastasis antedated the diagnosis of thyroid carcinoma and he had no clinically obvious thyroid swelling or regional lymphadenopathy.

Struma ovarii is a slow growing ovarian neoplasm within thyroid tissue because it is the only or the predominant (>50%) constituent. The ovarian thyroid is histologically and functionally identical to the cervical thyroid. The tumour is a highly specialized subclass of benign cystic teratoma; 95% remain benign while the remainder undergo malignant transformation, with peak frequency during the fifth decade of life.\(^ {25,26}\) The left ovary is more frequently affected estrogen receptors.\(^ {27}\) It is noteworthy that the lack of demonstration of estrogen and progesterone receptors in struma ovarii can be explained by the complete transformation of ovarian tissue into struma, as normal thyroid follicular cells do not express estrogen receptors.\(^ {27}\)

In conclusion, differentiated thyroid cancer can present with atypical manifestations. A routine preoperative physical examination of the thyroid gland should be done in all cases of metastatic lesions of unknown origin. Clinical suspicion and aggressive work-up and treatment are usually rewarding. The high incidence of metastatic disease in an iodine deficiency area like ours is postulated due to the advanced stage at presentation or inherent aggressive biological behavior.

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