

LETTERS TO THE EDITOR

Mixed medullary and papillary thyroid carcinoma: A stepwise diagnosis

Dear Editor,

Medullary thyroid carcinoma (MTC) is an unusual thyroid malignancy and has a distinctive behavior, far different from the commonest papillary thyroid carcinoma (PTC). The concurrence of the two types in the same tumor is a seldom event found only in case reports and in 1% of all thyroid malignancies [1]. MTC arises from the parafollicular C-cells, which have neural-crest origin, while PTC originates from the main thyroid follicular cells.

A 59-year-old woman was admitted for the management of a long-standing multinodular goiter. Serum thyroid hormones, thyroid stimulating hormone (TSH) and anti-thyroglobulin antibodies (Anti-Tg Ab) were normal. Calcium, phosphorus, parathyroid hormone and carcinoembryonic antigen (CEA) were unremarkable, but calcitonin level was 45ng/L (normal range <5.8ng/L). Moreover, she was investigated for MEN with negative results. Clinical examination and imaging were negative for metastatic disease. The patient underwent an uneventful total thyroidectomy with central compartment (level VI) lymph nodal dissection.

Histopathology revealed a 0.7cm left nodule with thyroid follicles with mild mitotic activity, minimal necrosis and ground glass nuclei (Figure 1a). In the stroma there were solid aggregations of round to polyhedral to plasmacytoid cells having moderate to abundant granular cytoplasm. The distinctive characteristic of calcifications in the form of psammoma bodies was also notified. The presence of dual tumor population was confirmed on immunohistochemistry as the neoplasm was strongly positive for chromogranin A, synaptophysin, calcitonin (Figure 1b) and CEA, while it remained negative for thyroglobulin. The above led to the diagnosis of mixed MTC/PTC. Five lymph nodes were found negative for metastasis. Genetic analysis of RET oncogene was negative. Calcitonin levels returned to normal and the patient was started on suppression therapy with levothyroxine. The patient remains disease free and asymptomatic one year later on follow-up.

The variant of mixed medullary-follicular carcinomas are unusual neoplasms, combining the morphological and immunohistochemical properties of both parafollicular and follicular cell lineages [2]. A WHO definition is the

base for their proper diagnosis [3]. It should be emphasized that this case was not a collision tumor of the two thyroid carcinomas, but a totally mixed tumor showing dual differentiation.

As most thyroid cancers, these tumors arise more frequently in women, remain asymptomatic or can present with a palpable neck mass and treatment is mainly surgical. It is interesting that lymph node metastasis can have a mixed variant of MTC and PTC cells in the same lymph node underlying that histopathological examination of lymph nodes should be very meticulous. Pathogenesis remains unknown and the correct diagnosis should follow a stepwise approach. After the classic hematoxylin/eosin staining and examination, immunohistochemistry is the key for guiding the histopathologist towards mixed characteristics of MTC and PTC [4].

Classically, patients with PTC have favorable survival rates while MTC is considered to have a worse prognosis, with high recurrence incidence and mortality. Prognosis, as expected, of mixed MTC/PTC depends upon the medullary component, and in conclusion, careful histopathological examination guides to correct diagnosis and determines clinical management [5].

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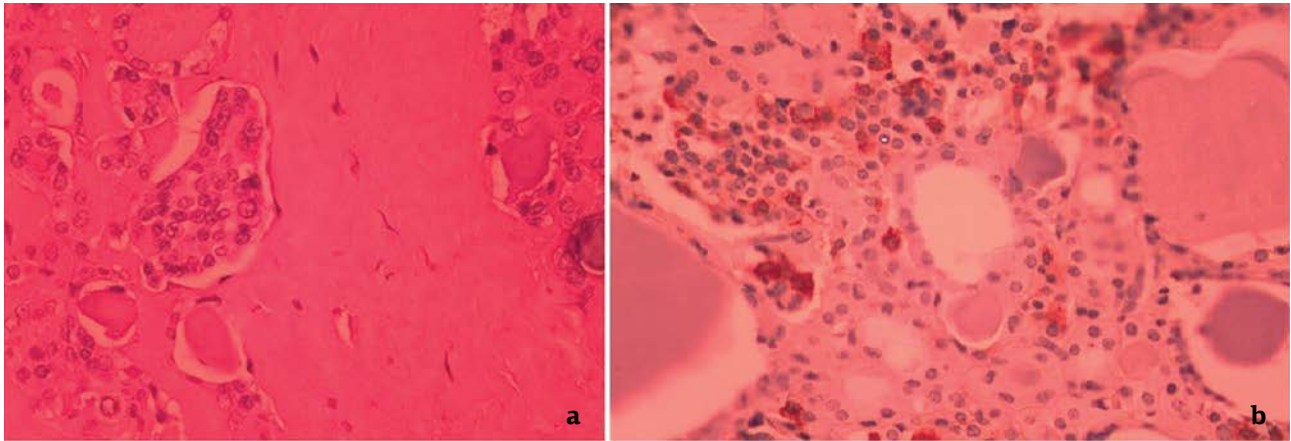


Figure 1. a. Histological section of thyroid nodule showing a papillary focus of cells with ground glass nuclei (H-E x400). **b.** Histological section of thyroid nodule showing calcitonin positive C-cells (Calcitonin x 400).

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Less is more: salvageability as the new creed in surgery of colorectal liver metastatic disease

Dear editor,

The mainstay of treatment for colorectal liver metastases (CLM) is surgical excision with negative microscopic margins (R0 resection), while leaving an adequate functional liver remnant. The extensive surgery that is often required, however, may be associated with short-term suffering from the surgery and related complications, permanent loss of function, readily visible deformity, high economic cost and even death. Previously, hepatectomy was only performed in selected patients who had a small number and size of nodules. However, advances in surgical techniques offered to patients with advanced CLM pushed the frontiers of resectability [1].

The last decade, Parenchymal-Sparing Hepatectomy (PSH) has been introduced as an alternative approach to major hepatectomy to achieve short-term disease control and preserve uninvolved functional liver parenchyma (salvageability). This approach was thought to be correlated with increased rate of recurrence due to closer margins and a greater amount of "at risk" future liver remnant in which metastasis could seed. A recent study, though, demonstrated the striking

finding that PSH did not impact negatively on overall, recurrence-free and liver-only recurrence-free survival and was a beneficial factor for candidacy for repeat hepatectomy, without increased risk of recurrence [2]. Moreover, repeat resection in patients with recurrent disease after CLM resection is shown to offer the potential for cure without increasing perioperative mortality and morbidity rates [3].

Another parameter that should also be highlighted is the disability that the surgical treatment of colorectal cancer (CLC) can cause. Achieving full recovery after CLC surgery means a return to normal physical and psychological health and to a normal social life. Until now, recovery data focused on time to discharge rather than long-term functionality including return to work. In Europe, one-quarter of patients diagnosed with CLC are under the age of 65, with the age for state pension eligibility to have risen to 67. This will significantly increase the number of patients of working age diagnosed with CLC [4]. For patients diagnosed with CLC whilst in employment, full recovery including return to work is vital in maintaining socio-economic status. A recent study demonstrated that the total number of disability-adjusted life years (DALY) lost from cancer in middle-aged and

older adults was 34,474 (382 per 1000 individuals), with CLC being responsible for 15.3% of that loss. Even if the burden of disease because of cancer is predominantly caused by mortality, CLC has also sizeable consequences for disability. In the same frame, another study demonstrated that more than one third of the employed CLC patients could not return at work 1 year after surgery for CLC [5].

All in all, we suspect that salvageability, as a treatment doctrine, seems to reach the silver lining in CLM disease since it offers non-inferior oncological outcomes, less perioperative risk and surgical stress, that in turn, is correlated with less postoperative disability compared with current standard of care. Thus, prospective studies and clinical trials evaluating the multiple beneficial role of salvageability surgical strategy in CLM disease are mandatory to support or reject our hypothesis.

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Cervical cancer screening problem: The social and cultural matters in Iran

Dear Editor,

Tsikouras et al. have described well the screening of cervical cancer in developing countries and in different ages [1]. Based on recent publications cervical cancer is the third most frequent cancer in women around the world and the eleventh most common cancer among Iranian women [2]. Previous studies in Iran showed that 80% of women diagnosed with invasive lesions never experienced an early detection. The National Cancer Registry reported that the death rate of this cancer among women diagnosed with invasive disease is about 40%, while some studies reported an increase in abnormal Pap smear in Iran during the past few years [3]. This important health problem caused the Ministry of Health and Medical Education in Iran to recommend the following official screening program that included Pap smear test and HPV vaccination, the goal being the early disease diagnosis, allowing thus treatment administration to decrease morbidity and mortality rates and also to prevent disease development. Previous studies have shown that poor knowledge about Pap test would cause inadequate compliance, making this test unwelcoming by women [3]. However, regular cervical cancer screening in develop-

ing countries and Iran is facing a number of challenges [4]. There are many barriers to early detection of cervical cancer in Iran and other developing countries, including individual and socio/cultural reasons. Low knowledge about Pap test is a serious factor, but socio/cultural attitudes are more important barriers in delaying detection of invasive cervical cancer, and perhaps are those causing refusal of screening. Bayrami et al.[4] showed that most women aren't familiar with warning signs of this cancer and knowledge about Pap test is very low. For example, many women don't like to talk about their genital tract diseases such as cancer and sexually-transmitted diseases. Since more than 500-900 middle-aged women are diagnosed with invasive cervical cancer every year in Iran [3], an organized cervical cancer screening is a necessity for Iranian women and we suggest to start screening tests for women from 21 years old according to international guidelines. The better way to inform people is by mass media about the symptoms and signs of cervical cancer to increase people's knowledge and make it easier for women to express their genital problems.

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Regional metastatic disease caused by malignant blue naevus

Dear Editor,

A 73-year-old female patient with a regional metastatic disease from melanoma was treated at our Clinic several times. Five years earlier, a malignant blue naevus on the left lower leg was diagnosed and operated. Two years after the radical surgical excision of the primary tumor, multiple subcutaneous nodules at the level of middle and distal third of the lower leg appeared. Due to her poor general condition and comorbidity, neither adjuvant therapy nor regional chemotherapy with isolated limb infusion could be applied. A complete circumferential suprafascial excision of the skin on the lower leg was performed along with lymph node dissection of the left groin. The defect was covered with split thickness skin grafts. For six months after the operation, the patient was without obvious clinical manifestations of the disease. Following this period, a small single, and afterwards multiple cutaneous and subcutaneous lesions began appearing in the region of the ankle joint, knee and thigh, which were successively removed with local excisions. In the terminal stage of disease, multiple and diffuse cutaneous and subcutaneous lesions formed along the limb with metastatic ulcerations at the level of the previous primary tumor and skin transplants (Figure 1). It was only at this stage of disease that hematogenous metastases of the liver and lung had been detected by PET/ CT scan. The patient lived for an additional 5 months.

The histopathologic findings of the primary tumor showed malignant spindled melanocytes arising from an atypical cellular blue naevus. The course of treatment and final clinical outcome were influenced by late diagnosis of disease (long-term evolution for more than 10 years) and a tumor diameter greater than 2.5 cm with proliferation of malignant cells into the subcutaneous tissue. Further disease spread was followed by lymphovascular and perineural invasion and locoregional dissemination.

A comprehensive review article identified 109 patients with malignant blue naevus. The most common lo-

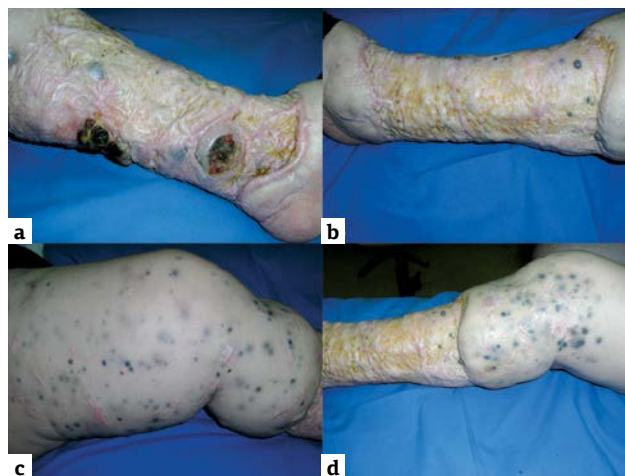


Figure 1. a. Lower leg and ankle joint – medial side. b. Lower leg and knee – lateral side. c. Thigh and knee – medial side. d. Lower leg and ankle joint – lateral side.

calization of these lesions was the head and neck region (52 cases), while only 11 patients had the tumor localized on the lower extremity [1]. It is known that the most frequent anatomical sites for melanoma in female patients are extremities, which does not correlate with the data for malignant blue naevus [2].

Although there is no accurate guideline for patients with malignant blue naevus, a radical surgical excision with sentinel lymph node biopsy is essential for treatment. Therapeutic dissection of lymph nodes is indicated in case of clinically positive lymph nodes or positive sentinel lymph node. Molecular detection of BRAF gene mutations should be done in selected patients. In the clinical follow-up, possible further treatment is dependent on the stage of disease which may include immunotherapy, chemotherapy, radiotherapy or isolated limb perfusion [3].

A recent study has shown similar clinicopathologic behavior and survival between patients with melanoma and those with malignant blue naevus, so they could be considered as the same type of cancer [4]. Therefore, the treat-

ment algorithm for these malignant skin tumors should not diverge. Management of malignant blue naevus should follow appropriate melanoma management guidelines [5].

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Intrascotal metastasis of bladder transitional cell carcinoma as initial presentation of the disease

Dear Editor,

Bladder transitional cell carcinoma (BCa) is nowadays the 11th most commonly diagnosed type of cancer worldwide with a higher prevalence in males. The highest incidence is observed in Western Europe, North America and Australia. It is estimated that 25% of BCa patients present with muscle invasive disease at the time of diagnosis while 10% may also have metastasis [1]. Most common sites of metastasis from BCa are lymph nodes, lungs, liver, peritoneum and intestine [2]. The aim of this article is to present an extremely rare case where testicular metastasis was the initial presentation of BCa.

A 62-year-old male with no previous history of BCa presented to our department with a painless palpable firm mass in the right testis. The patient was a former smoker without any concomitant diseases apart from lower urinary tract symptoms for which he was under tamsulosin treatment the last two years. Physical examination confirmed a painless firm mass located in the right testis. AFP, hCG and LDH were within normal limits. Scrotal ultrasound showed total heterogeneity of the right testicle with increased internal vasculature suggesting neoplasia (Figure 1). Abdominal ultrasound didn't show abnormal findings and urinalysis was positive for deepstick haematuria. Based on the above findings surgical intervention was proposed and the patient underwent radical right orchidectomy. Histological examination revealed high grade transitional cell carcinoma located to the right testis. After



Figure 1. Scrotal ultrasound showing total heterogeneity of the right testicle.

a few days, the patient underwent cystoscopy under anesthesia and biopsies were taken from the bladder mucosa as well as from the prostatic urethra. Pathology report confirmed high grade BCa in all bladder and prostate biopsy samples, plus in situ carcinoma. The patient presented with acute urine retention a few days later and a transurethral resection of the prostate was performed confirming prostate invasion from high grade BCa. Abdominal and thoracic CT scans were also performed [WITH WHICH RESULT?] and the patient was referred to the oncology department and is now under cisplatin-based chemotherapy.

The incidence of metastasis to the testis ranges from

0.3 to 3.6% with most frequent primary site being the prostate followed by lung, melanoma, large intestine and kidney [3]. Although BCa usually metastasizes to lymph nodes, lung, liver, peritoneum and intestine there are reports of unusual metastatic sites including heart, brain, kidney, spleen, pancreas, meninges, uterus, ovary, prostate, and testes in approximately 1-8% of metastatic BCa patients [2,4]. More specifically, testicular metastasis arising from BCa is extremely rare and only a few cases are reported in the literature. Testicular involvement usually occurs as a direct spread through the ejaculatory ducts when the disease is also involving the prostate. In most cases reported in the literature, metastasis was diagnosed after the diagnosis and treatment of the primary tumor with only one case reporting synchronous solitary spread to the testis. These types of metastasis are more likely due to hematogeneous spread rather than direct invasion through the prostate [5]. As a result, it is quite important to presume that all testicular masses in patients with history of BCa are considered metastatic unless proven otherwise by surgery. To our knowledge, this is the first case when initial presentation of BCa was a testicular metastasis.

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Chemotherapy and loss of fingerprint; problematic issue beyond the side effect

Dear Editor,

Hand-foot syndrome (HFS) is a common and sometimes serious adverse response to several chemotherapeutic drugs. HFS has been described in patients taking capecitabine monotherapy as well as in combination regimens. Other drugs, including cytarabine, doxorubicin, epirubicin, 5-fluorouracil, high-dose interleukin-2, fluorodeoxyuridine, hydroxyurea, mercaptopurine, cyclophosphamide, and docetaxel, are known to cause HFS [1]. Newer drug classes associated with HFS include epidermal growth factor receptor inhibitors and multikinase inhibitors [2]. HFS, or palmar-plantar erythrodysesthesia, is a distinct localized skin reaction characterized by erythema, numbness, tingling, and either dysesthesia or paresthesia, especially on the palms or soles. Symptoms include pain and swelling, and can progress to blistering, desquamation, and ulceration [1]. Loss of fingerprint by chemotherapy has been reported in three case reports [3-5]. These case reports prompted us to believe that, in addition to providing advice about skin care and cautioning patients

to report dermatologic issues as soon as they develop, patients should also be informed about the possible loss of fingerprints. Over many years there has been a rapid increase in the biometric security measures by checking fingerprint. These may include unlocking smart phones to border control. Some work places force you to scan your fingerprint to the scanner. If you have lost your fingerprint, you would not be able to scan your finger and as a result many issues may occur, such as not being able to go through the barriers at a work place that requires you to scan your fingerprint to go through. Another issue is about travelling patients. They would be asked to provide their fingerprint in international airports in some countries, but they cannot because of the side effects of the drugs which led to the removal of the fingerprint.

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