Case Series

Simultaneous occurrence of follicular and papillary thyroid carcinomas in same thyroid lobe: A case series of six patients from Qatar

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1. Background

Although composite thyroid carcinomas have been reported in the literature, the simultaneous occurrence of multiple thyroid tumors of different histopathological types in the same thyroid lobe is a rare presentation and known as mixed, hybrid tumours or composite tumours [1]. About 71 cases of concurrent papillary thyroid cancer (PTC) and medullary thyroid cancer (MTC) have been reported [2], but cases of PTC and follicular thyroid cancer (FTC) presenting synchronously are much rarer [3–5] and signify the simultaneous occurrence of distinctly different entities. Well-differentiated thyroid carcinomas (e.g., PTC and FTC) are usually sporadic in most cases [6], and the coexistence of two independent and simultaneous follicular epithelial cell carcinomas, a papillary carcinoma and a follicular carcinoma, is extremely rare [7].

To the best of our knowledge this could be the first case series of simultaneous occurrence of two types of thyroid cancer (PTC and FTC) reported from the Middle East and North Africa region (MENA). One case report from the Middle East region had three types of thyroid cancer [6]. We report these cases due to the uniqueness of their histopathological findings and to debate their possible complex histogenesis. This case series report is in line with the updated consensus-based case series (PROCESS) guidelines [8].
crowding,
showed
2.

and
4
posterior
9
Hamad
Case

thyroid

revealed
benign
thyroid
with
chronic
lymphocytic
thyroiditis.
She
then
took
two
doses
of
radioactive
iodine
(30
mCi).
Follow
up
radioactive
whole
body
scan
showed
no
evidence
of
radioiodine
avid
local
or
distant
pathology,
and
follow
up
US
of
the
neck
showed
no
definite
residual
or
recurrence
in
the
thyroid
bed.
Laboratory
results
after
two
years
showed
very
low
thyroglobulin
(<0.1
ng/mL)
and
thyroglobulin
antibodies
(<0.9
IU/mL).

2.2. Case 2

A Sudanese
male,
61
year
old,
was
being
followed
up
at
the
urology
department
for
a
radical
prostatectomy
for
prostatic
cancer
that
was
followed
by
radiation
therapy.
During
follow
up,
CT
scan
of
the
chest
showed
an
incidental
finding
of
an
enlarged
right
thyroid
lobe
that
had
a
central
area
of
hypodensity.
The
patient
was
referred
to
our
thyroid
clinic.
On
examination,
we
found
a
right
thyroid
mass.
There
was
no
family
history
of
cancer
thyroid.
Investigations
showed
normal
TFTs.
Ultrasound
of
the
thyroid
gland
showed
enlarged
right
thyroid
lobe
(3.1
cm
antero-posterior
dimension)
that
contained
a
large,
mainly
isoechogenic,
heterogenous
nodule
occupying
almost
all
of
the
right
thyroid
lobe,
with
slightly
increased
peripheral
vasularity.
The
left
thyroid
lobe
measured
1.5
cm
(antero-posterior
dimension),
showed
normal
echotexture
and
normal
flow
on
colour
Doppler,
and
contained
multiple
small
nodules,
the
largest
of
which
appeared
cystic
in
the
lower
pole
measuring
1 \times 0.7
cm.
Ultrasound
guided
FNA
of
the
right
thyroid
raised
suspicion
for
folicular
neoplasm.
The
patient
underwent
right
hemithyroidectomy.
Histopathology
indicated
unifocal
FTC
(6 \times 3 \times 2.7
cm),
encapsulated,
uninvolved
margins,
angioinvasive
(focal
< 4
vessels),
no
lymphatic
or
perineural
invasion
and
no
extrathyroidal
extension.
Pathologic
stage
(pTNM,
AJCC
8th
Edition
[9])
was
pT3a
Nx.
The
specimen
was
also
sent
for
review
at
the
Mayo
Clinic
which
indicated
a
well-differentiated
foflicular
neoplasm
with
angioinvasion
and
capsular
invansion,
most
consistent
with
folicular
carcinoma,
with
a
separate
focus
of
papillary
thyroid
microcarcinoma
(3
mm),
pathologic
stage
pT1a
Nx
[9].
The
patient
underwent
completion
left
hemithyroidectomy.
Histopathology
indicated
nodular
hyperplasia
with
predominant
nodule
on
a
background
of
chronic
cancer
thyroiditis.
The
patient
received
high
dose
(100
mCi)
radioactive
iodine
ablation
(RAI).
Follow
up
whole
body
scan
3
months
later
showed
no
evidence
of
either
residual
thyroid
tissue
or
metastatic
tumor;
and
follow
up
US
of
the
neck
year
later
showed
no
thyroid
tissue
residual,
or
focal
lesion
at
the
thyroid
bed.
Laboratory
results
after
15
months
showed
very
low
thyroglobulin
(<0.2
ng/mL)
and
thyroglobulin
antibodies
(<0.9
IU/mL).

2.3. Case 3

A Sudanese
male,
59
year
old,
presented
to
our
thyroid
clinic
with
recurrent
multinodular
goiter
involving
mainly
the
isthmus
and
left
lobe.
He
had
history
of
thyroid
surgery
20
years
back
in
Sudan,
no
history
of
irradiation
therapy
and
no
family
history
of
cancer
thyroid.
On
examination,
the
patient
was
clinically
 euthyroid,
with
a
huge
frontal
neck
swelling
(15 \times 7
cm).
Investigations
showed
normal
TFTs.
US
of
the
thyroid
showed
absence
of
right
thyroid
lobe,
and
the
left
lobe
and
isthmus
were
enlarged
with
multiple
nodules,
showing
solid
complex
echotexture
with
partially
ill-defined
margins
and
central
areas
of
anechoic
components
suggestive
of
cystic
degeneration,
the
largest
of
which
measured
4.1 \times 2.8
cm.
Ultrasound
guided
FNA
showed
follicular
lesion
of
US
on
a
background
of
lymphocytic
thyroiditis.
Completion
left
thyroidectomy
was
done.
Histopathology
showed
FTC,
widely
invasive
(5
cm),
abutting
the
inked
anterior
margin
and
0.1
mm
from

2. Case presentations

2.1. Case 1

An
Egyptian
female,
31
year
old,
presented
to
our
thyroid
clinic
at
Hamad
Medical
Corporation
(bigest
tertiary
care
facility)
in
Doha,
Qatar,
with
left
neck
swelling
since
a
year,
increasing
in
size,
associated
with
mild
left
neck
pain.
She
had
no
history
of
irradiation
therapy
and
no
family
history
of
cancer
thyroid.
Examination
revealed
a
left
thyroid
nodule
(4 \times 3
cm)
that
moved
with
swallowing,
and
no
calculi
nodes.
Investigations
showed
normal
thyroid
function
tests
(TFTs).
Ultrasound
(US)
of
the
thyroid
revealed
a
large
left-lobed
thyroid
nodule
(5 \times 2.5
cm)
with
small
thin
peripheral
halo,
peripheral
and
central
vasularity
and
coarse
calcifications.
Ultrasound
guided
fine
needle
aspiration
(FNA)
showed
follicular
cells
of
determined
significance
(FLUS).
The
patient
underwent
left
hemithyroidectomy.
Post-operative
histopathology
showed
left
papillary
thyroid
carcinoma
(PTC)
(5 \times
4
cm)(Fig. 1)
and
follicular
tyroid
carcinoma
(FTC)(1.3
cm)(Fig. 2).
The
FTC
had
uninvolved
margins,
the
margins
were
close
to
the
posterior
and
anterior
margins
(within
0.1
mm),
and
AJCC
staging
[9]
was
pT1b,
N0.
The
PTC
histology
was
oncocytic,
with
G1,
well-
differentiated
histologic
grade,
as
adjacent
to
the
anterior
margin,
and
AJCC
pathologic
staging
[9]
was
pT1b,
N0.
Hence,
the
patient
underwent
completion
right
hemithyroidectomy,
and
histopathology
revealed
benign
thyroid
with
chronic
lymphocytic
thyroiditis.

Fig. 1. Papillary thyroid carcinoma with characteristic nuclear features (nuclear
crowding, overlapping, clearing, membrane irregularities and inclusions).

Fig. 2. Thyroid follicular carcinoma widely invading the thyroid capsule.
inked posterior resection margins, with lymphovascular invasion but no perineural or angioinvasion, no extrathyroidal extension, of stage pT3a pNx [9]. There was also a separate focus of PTC (greatest dimension = 1.5 cm) of stage pT1b pNx [9], abutting the inked anterior margin, with no lymphovascular, perineural or angioinvasion, no extrathyroidal extension. The patient was discussed at our thyroid multi-disciplinary meeting (MDT) and was categorized as high risk stratification (ATA 2015). He received RAI 100 mCi, then follow up US showed residual thyroid tissue, so the patient received another 30mCi RAI. Follow-up US of the neck after 22 months showed no residual thyroid tissue, and both thyroid beds were normal. Final laboratory findings showed thyroglobulin 3.6 ng/mL, and thyroglobulin antibodies 1.2 IU/mL.

2.4. Case 4

An Indian female, 56 year old, with Hodgkin’s lymphoma in remission since 2001. Presenting at our thyroid clinic, she had noticed a left side neck swelling since one year and started feeling pressure symptoms since one month. Examination revealed a bilateral neck swelling that moved with swallowing. She had no history of irradiation therapy and no family history of thyroid cancer. Investigations showed normal TFFs. Follow up whole body fluoroodeoxyglucose positron emission tomography integrated with computed tomography (FDG PET CT) showed no signs of lymphoma relapse or lymph node or distant organ metastasis, but showed incidental highly FDG positive bilateral thyroid nodules. US of the thyroid showed left thyroid nodule (4.5 cm) with a smaller nodule within it with heavy rim calcification and solid component with microcalcification at the bottom. US of the neck also showed 2 hypoechoic nodules in the right lobe, the largest was ill-defined with coarse calcification measuring (7 × 7 × 10 mm). No suspicious lymph nodes were seen. Ultrasound guided FNA showed atypical follicular lesion of undetermined significance (AUS). The patient underwent total thyroidectomy, and histopathology showed FTC, minimally invasive and multifocal classical variant PTC. The FTC in the left lobe was unifocal (4.5 × 3.5 × 2.5 cm), minimally invasive, < 0.1 mm from the posterior margin, no perineural invasion or angioinvasion, but present lymphatic invasion, and no extrathyroidal extension. Pathologic stage was pT3a pNx [9]. The FTC was multifocal with nodular hyperplasia, present in both lobes (first focus in right lobe 1 × 0.8 × 0.7 cm, 0.1 mm from the anterior margin; second focus in right lobe 0.5 cm in maximum dimension; third focus in left lobe 0.6 cm in maximum dimension). No lymphatic, perineural or angioinvasion or extrathyroidal extension. Pathologic stage was mp T1a pNx [9]. The patient was discussed in our thyroid MDT meeting and categorized as high risk stratification (ATA 2015) eligible for high dose radioactive iodine ablation. The patient travelled out of the country and was lost to follow up.

2.5. Case 5

A Filipina female, 35 years old, was referred to our thyroid clinic with multinodular goiter and a dominant nodule in the right lobe. She complained of mild hoarseness of voice, but no pressure symptoms. There was no family history of thyroid cancer and no history of irradiation. On examination, there was right thyroid lobe enlargement. She was clinically euthyroid, with normal TFFs. US of the neck showed heterogeneous echopattern with mild increased vascularity and multiple nodules with calcification in both lobes. There were at least three nodules in the right lobe, the largest complex nodule was in the lower pole (2.1 × 1.9 cm), and another solid nodule with calcification in the upper pole (1.8 × 1 cm). The left lobe also showed multiple nodules, where the largest complex nodule measured 4.8 × 2.5 cm. There were no significantly enlarged cervical lymph nodes. FNA (ultrasound guided) showed right thyroid nodules comprising malignant cells consistent with PTC. The patient underwent total thyroidectomy. Histopathology showed right micro PTC, multifocal (two foci), largest was at least 0.8 cm, with uninvolved margins, no lymphovascular, perineural, or angioinvasion and no extrathyroidal extension, and pathologic staging was pT1aN0 [9]. Histopathology also showed right FTC, unifocal, at least 1.3 cm, with uninvolved margins, no lymphovascular, perineural or angioinvasion and no extrathyroidal extension, and pathologic staging pT1BNO [9]. The patient was discussed at our thyroid MDT meeting and categorized as high risk stratification (ATA 2015) eligible for high dose radioactive iodine ablation. The patient travelled out of the country and was lost to follow up.

2.6. Case 6

A Qatari female, 52 years old, presenting with a neck swelling a year ago, associated with some pain on swallowing, no compression symptoms, underwent an FNA in Thailand that showed suspicious follicular lesion and was hence referred to our thyroid clinic. On examination, there was a nodular swelling of the thyroid gland, but it was not tender. US of the thyroid showed multiple right lobe solid thyroid nodules, largest was complex, predominantly solid (15 × 26 mm), showing rim calcification, cystic change, and intra nodular vasularity. The left lobe measured 21 mm, and had an isoechoic thyroid nodule, (17 × 20 mm) showing hypoechoic halo and intra nodular vascularity. There were a few cervical lymph nodes with preserved echogenic hilum. Ultrasound guided FNA was repeated at our institution, the right thyroid nodule was FLUS, and the left thyroid nodule was also FLUS. The patient was discussed at our thyroid MDT and planned for total thyroidectomy which was undertaken. Histopathology revealed right lobe single focus FTC (2.7 × 1.5 × 1.5 cm) with capsular invasion, margins were free of carcinoma, < 0.5 mm from both anterior and posterior margins, no lymphovascular, perineural, or angioinvasion no extrathyroidal extension, and pathologic staging was pT2NX [9]. There was also a single focus papillary thyroid microcarcinoma, follicular variant (0.8 × 0.6 × 0.4 cm), non-capsulated, margins were uninvolved by the carcinoma, closest margins were the anterior and posterior margins with < 0.5 mm clearance, no lymphovascular, perineural, or angioinvasion, no extrathyroidal extension, and pathologic staging was pT1aNX [9]. In addition, the histopathology showed an adenomatoid nodule in the left lobe (third lesion), classified as pT1a [9]. The patient was discussed at our thyroid MDT meeting, and she was straified as intermediate risk (ATA guideline). She was planned for low dose RAI ablation and thyroid cancer surveillance with neck US and thyroglobulin tumor markers, and suppressive therapy with Levothyroxine. US of the neck post total thyroidectomy and RAI ablation showed soft tissue structures in both thyroid beds bilaterally that could represent residual or recurrent thyroid tissue, although the non stimulated thyroglobulin was very low (0.2 ng/mL) and thyroglobulin antibodies were negative. Table 1 depicts a summary of the six cases.

3. Discussion

PTC and FTC are both derived from thyroid follicular cells, where PTC is the most common and FTC the second most common of all thyroid carcinomas [10]. Both PTC and FTC are differentiated thyroid carcinoma that comprises 90% of all cases of thyroid cancer (incidence about 0.5–10 new cases per 100,000 population globally) [11–13]. Thyroid carcinomas account for about 4% of new cancer cases in the United States [14]. In Qatar, thyroid cancer is the sixth most common cancer across all nationalities and genders; the second most common malignant cancer among females of all
nationals; and the second and fourth most common malignant cancer among non-Qatari and Qatari females respectively [15].

Despite the relatively high prevalence of thyroid cancer, the synchronous co-occurrence of multiple, distinct sub-types of primary thyroid carcinomas is uncommon. In the literature, up to 2017, very few cases of synchronous PTC and FTC have been reported, including three with additional medullary carcinoma, one with additional undifferentiated carcinoma [3–6,16,17], and in one patient, follicular carcinoma, an occult papillary carcinoma and a medullary carcinoma [7].

Table 1 depicts the summary of characteristics of our six patients with concurrent FTC and PTC. In terms of age, three of our patients agreed with the age range of the published literature: however, one patient was 31 years old, younger than the mean age. As for invasiveness, among the six cases we observed, the PTC did not exhibit lymphatic,peri-neural or angio-invasiveness; however, the FTC in two out of the six patients (Cases 3 and 4) had lymphatic invasiveness, and in one patient, it showed angioinvasion (Case 2).

In terms of origin, differentiated thyroid carcinomas, e.g., FTC and PTC originate from follicular epithelial cells derived from median endodermal analogues [18]. Whilst the synchronous coexistence of more than one type of thyroid cancer could be a coincidence, several theories have been postulated as potential explanations for such synchronous coexistence. These include propositions that they might be linked to the presence of RET protooncogene mutation in both papillary and medullary thyroid cells [19]; common stem cell theory [20]; or common tumorigenic stimulus such as radiation exposure that promotes the malignant transformation of both endodermal and neural crest-derived cell lines [21]. Reports also postulate that the pathogenetic mechanisms of hybrid tumors include collision theory that proposes simultaneous multifocal origin from different cell clones [22], suggesting that two independent tumours are located in the same lesion by simple coincidence [18]; or hostage theory that proposes that adenomatous areas are sequestrated by another tumour type, though the exact etiology is elusive [1]. Where components were separated by normal thyroid tissue, others suggested that the occurrence of e.g., concurrent MTC/PTC is mostly a simple reflection of incidental papillary micrcarcinoma, and that concurrent MTC and PTC in the same thyroid should be considered as coincidental [18]. In terms of laterality, five of our cases had both the FTC and PTC in the same lobe. In addition, Case 4 had PTC in both lobes. Likewise, three of our patients (Cases 2, 4 and 5) had an FTC and a micro PTC in the same lobe (PTC measuring from 0.3–1 cm) suggesting that the PTC in these cases was incidental.

As for the pathological assessment, all the patients presented in this case series were examined by the same pathologist at the same laboratory in the same institution, in agreement that cautious and vigilant pathological assessment is critical in disclosing such patterns of pathology. Such vigilance is reflected in our pathology assessment of this case series that involved undertaking many ultra-thin sections that enabled the detection of micro PTC.

As regards to staging and risk prediction, in line with others, we undertook AJCC staging system and ATA stratification prediction system as they are the best predictors of mortality and recurrence respectively [23]. We also employed the AJCC 8th edition that better differentiates differentiated thyroid carcinoma (DTC) risk recurrence for early stages of disease compared with the 7th edition [24].

In terms of treatment, prognosis and survival, we instigated prompt treatment, and four of six patients were cured from the disease, in agreement with that DTC is usually curable when discovered at an early stage [25], and that thyroid malignancies have good long-term prognosis, as early and appropriate treatment yields good results [26]. Likewise, with full preoperative evaluation and stringent follow-up after surgery at our tertiary care institution, for
four patients in this series, we observed no recurrence and good survival, in support that the prognosis for DTC is excellent after appropriate surgical treatment, thorough preoperative assessment and strict postoperative follow-up [27]. Two of our patients travelled out of the country and were lost to follow up. In Qatar, the 3-year survival from malignant thyroid cancer during the period 2013–2015 was 90.0% (47.3–98.5%) [15]. Our findings support that the prognosis of differentiated thyroid carcinoma is favourable, with a 10-year survival rate of 80–95% [28], and that earlier detection of small differentiated thyroid cancer with less extensive disease and standardization of treatment may contribute to the decreased disease-specific mortality of such patients [29].

4. Conclusions

The patients presented in this case series had different ethnicities, and all had concurrent FTC and PTC in the same thyroid lobe. No apparent cause was found. Four of the six patients were cured, with no recurrence and good survival, whilst the remaining two patients travelled out of the country and were lost to follow up. Endocrinologists and pathologists should be vigilant, aware of and suspicious to the possible simultaneous occurrence of these types. Given the very few cases reported in the literature, further search for the unusual simultaneous occurrence of FTC and PTC is warranted.

Declaration of Competing Interest

Nothing to declare.

Sources of funding

Nothing to declare.

Ethical approval

Approved by medical research center, Hamad Medical Corporation reference number (MRC 17256/17).

Consent

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

Two patients travelled out of the country after surgery. Written informed consent was not obtained from these patients. The head of our medical team has taken responsibility that exhaustive attempts have been made to contact the family and that the paper has been sufficiently anonymised not to cause harm to the patients or their families. A copy of a signed document stating this is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Abdelrahman Abdelaal: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - review & editing. Walid El Ansari: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. Abdelrahman Abbasheib: Data curation, Writing - review & editing. Hanan Farghaly: Data curation, Validation, Writing - review & editing. Abdelhakem A.M. Tabeb: Data curation, Writing - review & editing. All authors read and approved the final manuscript.

Registration of research studies

Not first in Man, hence UIN not required.

Guarantor

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