A case of follicular thyroid carcinoma with bizarre nuclei and discussion of atypia in thyroid gland disease

Paul Hankinson
Gayani Pitiyage
Stuart Richards
Fawzia Tahir

Abstract

The presence of nuclear atypia is a potential pitfall in thyroid pathology with several causes ranging from benign disease to aggressive malignant neoplasms. Here we present a case of follicular thyroid carcinoma with bizarre nuclear atypia. Assessment of the type and location of the nuclear atypia as well as select molecular testing aided in diagnosis of this case, excluding other entities such as dyshormonogenetic goitre, papillary thyroid carcinoma, anaplastic thyroid carcinoma and *DICER1* mutated follicular thyroid carcinoma (a recently described entity in the literature). An awareness of the diverse nuclear features and the causes of nuclear atypia in thyroid disease can prevent misinterpretation of this feature reducing the risk of overdiagnosis of malignancy in tissue and cytology specimens.

Keywords Endocrine atypia; endocrine pathology; head and neck pathology; thyroid gland pathology

This Short Case is brought to you in association with the Pathological Society of Great Britain and Ireland. Each month we feature a Short Case written by a member of the Trainees' Subcommittee of the Pathological Society of Great Britain and Ireland. This case, including its scanned slides, is published on the Pathological Society's website www.pathsoc.org/index.php/trainees/case-of-the-month (previous cases can be accessed by members via the education portal login). The Short Case includes a series of Test Yourself Questions at the end to check your understanding of the case. We hope you enjoy reading it.

Pathological Society
Understanding Disease — Guiding Therapy

Case report

A 54-year-old female patient presented with a left thyroid gland mass. She had no other symptoms. Two thyroid fine needle aspirates were performed on the nodule, both diagnosed as in keeping with a follicular thyroid lesion (Thy3f). The patient proceeded to a left hemithyroidectomy. Macroscopically, the hemithyroid measured 65 × 40 × 32 mm and weighed 33.5 g. On slicing a unifocal, firm, pale tan nodule was identified which measured 54 × 30 mm.

Microscopically the tumour was encapsulated with a micro- and macrofollicular architecture and lacked papillary thyroid carcinoma (PTC) nuclear features. Insular, trabecular and solid growth patterns were not identified. Multifocal capsular invasion (Figure 1a) and significant vascular invasion within the tumour capsule (Figure 1b) was observed. There was no extrathyroidal extension. No lymph nodes were submitted, and the tumour was closely excised from the peripheral margins. Interestingly, numerous foci of large hyperchromatic cells with bizarre nuclear atypia were seen including multinucleated tumour cells (Figure 1c and 1d). However, there was no evidence of necrosis, and mitotic activity was low, (<3 mitoses/2 mm^2). Immunohistochemical analysis showed preserved TTF-1 staining in the bizarre nuclei (Figure 1e), with a low Ki-67 proliferation rate (Figure 1f). Targeted next generation sequencing did not detect oncogenic variants or rearrangements of *the BRAF, HRAS, KRAS, NRAS, RET, TP53, ALK, RET, NTRK1, NTRK2, NTRK3* or *DICER1* genes. A diagnosis of encapsulated angioinvasive follicular thyroid carcinoma with bizarre nuclei was given (TNM8 classification: pT3a, R0). These bizarre nuclei are most likely due to degenerative/endocrine atypia. Also noted was an incidental 2 mm classic PTC.

Discussion

There are several potential reasons for nuclear atypia within a thyroid lesion. Identification of the cause is important for prognostication and treatment decisions. Bizarre nuclei can be seen in a range of benign processes (dyshormonogenetic goitre, follicular thyroid adenoma with endocrine atypia), treatment effect (for example following radioactive iodine), malignant neoplasms (follicular thyroid carcinoma with endocrine atypia) and frequently fatal aggressive malignant entities (anaplastic thyroid carcinoma, ATC). It is therefore crucial to differentiate bizarre nuclear atypia from the atypia of aggressive malignancies, especially in biopsy samples. This includes distinction from the nuclear atypia of PTC. This is usually straightforward, as the morphological features of PTC nuclei differ significantly from those of bizarre nuclei.

Paul Hankinson *BMedSci BDS MFDS RCPS (Glasg) Speciality Registrar Oral and Maxillofacial Pathology, Unit of Oral and Maxillofacial Pathology, The School of Clinical Dentistry, Faculty of Health, University of Sheffield, Sheffield, UK. Conflicts of interest: none declared.*

Gayani Pitiyage *FRCPath PhD Consultant Head and Neck and Endocrine Pathologist, St George's University Hospital NHS Foundation Trust, London, UK. Conflicts of interest: none declared.*

Stuart Richards *FRCSEd (ORL-HNS) DLO Consultant ENT Surgeon and Director of Undergraduate Medical Education, The Rotherham NHS Foundation Trust, South Yorkshire, UK and Honorary Senior Lecturer, University of Sheffield, Sheffield, UK. Conflicts of interest: none declared.*

Fawzia Tahir *MBBS FRCPath Consultant Histopathologist and Lead in Endocrine Pathology, Department of Histopathology, Sheffield Teaching Hospitals NHS Foundation Trust, South Yorkshire and Bassetlaw Pathology, UK. Conflicts of interest: none declared.*

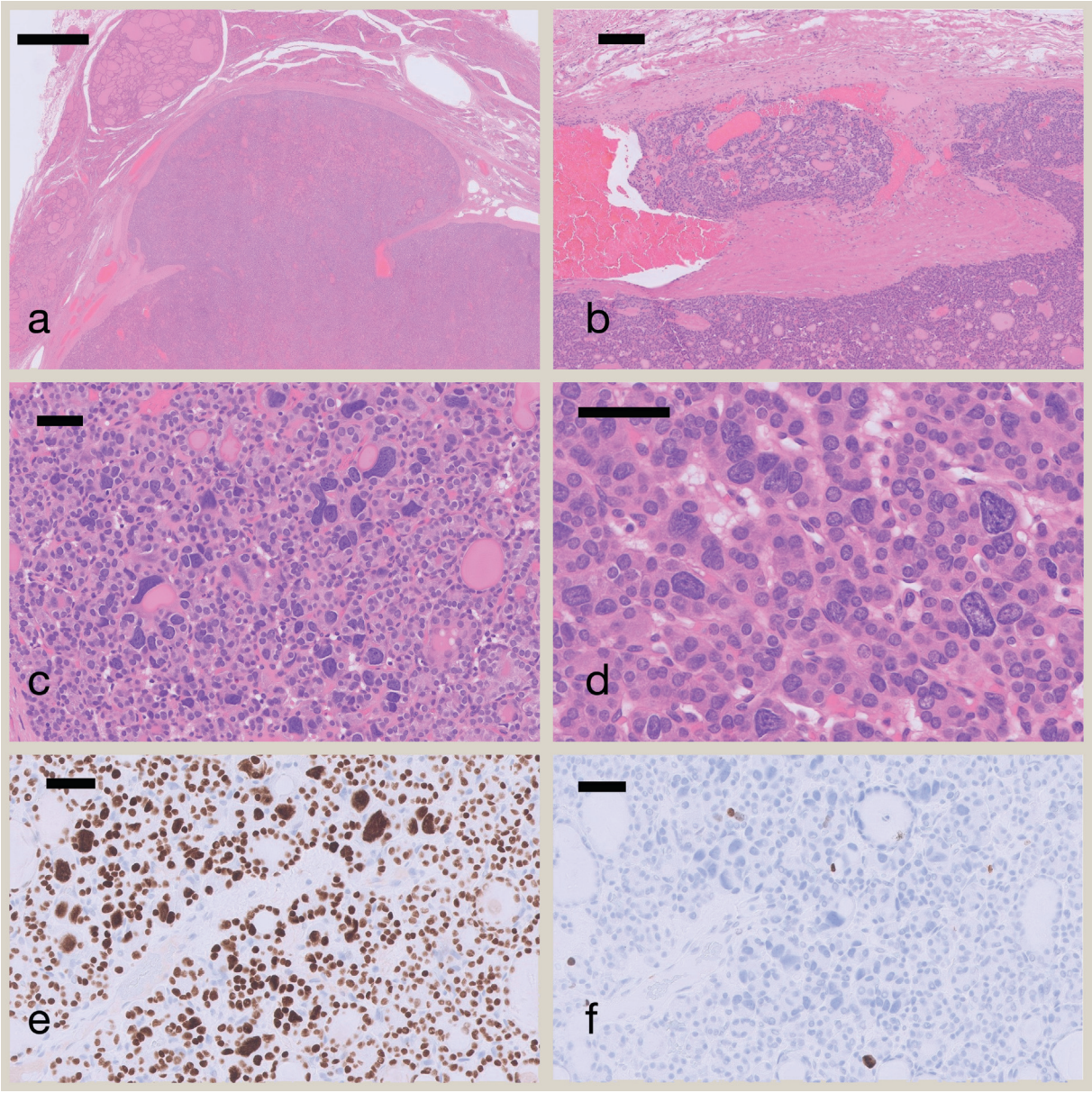

Figure 1 Photomicrographs of follicular thyroid carcinoma with bizarre nuclear atypia. (**a**) Photomicrograph demonstrating capsular invasion (scale bar 2 mm), (**b**) photomicrograph demonstrating angioinvasion (scale bar 200 μm), (**c**) photomicrograph showing a focus of bizarre nuclear atypia (scale bar 50 μm), (**d**) photomicrograph showing a further focus of bizarre nuclear atypia (scale bar 50 μm), (**e**) photomicrograph showing expression of TTF-1 in the atypical cells as well as the background neoplasm (scale bar 50 μm), (**f**) photomicrograph of Ki67 immunohistochemistry showing a low proliferation index, including in the atypical areas (scale bar 50 μm).

Bizarre nuclear atypia has been recently reported in follicular thyroid carcinomas with *DICER1* mutations,[1] prompting molecular testing in this case, though no *DICER1* mutation was detected. Given the significant implications of *DICER1* germline mutations, molecular testing should be considered in thyroid carcinomas with unusual histological features or presentation in childhood.[1,2]

Dyshormonogenetic goitre can be excluded by the location of the atypia, which is seen in the background thyroid follicular tissue rather than within the lesion itself. Other features of dyshormonogenetic goitre include nodular follicular thyroid disease with scant colloid as well as hypothyroidism.[3]

Endocrine atypia is a well-known phenomenon seen in endocrine organs including thyroid, parathyroid and adrenal tissue. It may be seen in normal thyroid gland, benign neoplasms such as thyroid follicular adenomas and malignant neoplasms.[3] Endocrine atypia appears as random scattered enlarged nuclei with hyperchromasia. Endocrine atypia may be misinterpreted in assessment of thyroid fine needle aspirate cytology, leading to excessive treatment in benign and hyperplastic disease with endocrine atypia.[4]

PTC and invasive encapsulated follicular variant of PTC have a distinct form of nuclear atypia.[3] Rather than enlargement, hyperchromasia and multinucleation these entities have well

defined and diffuse nuclear morphological features. This includes changes in size and shape (nuclear enlargement, overlapping), nuclear membrane irregularities (nuclear grooves, pseudo inclusions) and abnormal chromatin characteristics (nuclear clearing).[3] The atypia is usually more widespread throughout the lesion in these entities, rather than scattered as seen in the reported case.

Bizarre nuclear atypia and multinucleation can be seen in ATC.[3] It is important to rule out this entity as it has a dismal prognosis. Other 'high grade' features are usually seen with ATC, including necrosis, frequent mitoses and atypical mitotic figures. Immunohistochemistry can be useful. ATC will usually lose expression of TTF-1 and thyroglobulin, distinguishing it from other thyroid lesions with atypia which would retain expression.[5] Moreover, p53 will show strong extensive nuclear expression in 50% of ATC, with mutation frequently confirmed by next generation sequencing.[5] *BRAF V600E* and *RAS* mutations can also help support a thyroid origin in ATC.[3]

Conclusion

In conclusion, the presence of nuclear atypia is a potential pitfall in thyroid pathology with several causes ranging from non-neoplastic through to the most aggressive malignant neoplasms. Assessment of the location, histological pattern of the atypia, other clinical and histological features as well as select immunohistochemical and molecular testing can aid in diagnosis. ◆

REFERENCES

1 Monroe H, El Naili R. DICER1-Mutant thyroid carcinoma of unusual morphology: a follicular carcinoma with bizarre nuclei or a novel entity? *Am J Clin Pathol* 2023; **160**(Supplement_1)**:** S57.

2 Riascos MC, Huynh A, Faquin WC, et al. Expanding our knowledge of *DICER1* gene alterations and their role in thyroid diseases. *Cancers* 2024; **16:** 347.

3 WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet] [cited 23/04/2025 D]. (WHO classification of tumours series. 5th ed.vol. 10. 2025. Lyon (France): International Agency for Research on Cancer. Available from: https://tumourclassification.iarc.who.int/chapters/53.

4 Lam H, Saoud C, Shi Q, et al. Degenerative atypia in benign thyroid nodules: a potential diagnostic pitfall on fine-needle aspiration. *J Am Soci Cytopathol* 2023; **12:** 341–50.

5 Deeken-Draisey A, Yang GY, Gao J, et al. Anaplastic thyroid carcinoma: an epidemiologic, histologic, immunohistochemical, and molecular single-institution study. *Hum Pathol* 2018; **82:** 140–8.

Practice points

- A range of thyroid pathology can show nuclear atypia and the presence of atypia does not always help distinguish between benign or malignant disease
- The histological pattern of atypia is important, random nuclear enlargement is more likely to be seen in endocrine atypia, dyshormonogenetic goitre or anaplastic thyroid carcinoma, rather than the well-defined nuclear features of papillary thyroid carcinoma
- Endocrine atypia should be kept in mind when assessing thyroid fine needle aspirates as it is a potential pitfall which can lead to overtreatment

Self-assessment questions

1. Which thyroid lesion with nuclear atypia will be thyroglobulin negative?

A. Poorly differentiated thyroid carcinoma
B. Papillary thyroid carcinoma
C. Anaplastic thyroid carcinoma
D. Dyshormonogenetic goitre
E. Follicular adenoma with endocrine atypia

Answer: C

2. Which of the following is not a nuclear feature of papillary thyroid carcinoma?

A. Nuclear enlargement
B. Nuclear membrane irregularity
C. Nuclear pseudoinclusions
D. Nuclear chromatin clearing
E. Nuclear hyperchromasia

Answer: E