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Case Report

The input of GATA-3 in the identification of parathyroid carcinoma diagnosis: Case report with review of literature

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ABSTRACT

Introduction: and Importance: Parathyroid carcinoma is an exceptional cancer, with significant morbidity and mortality, associated with parathyroid hormone (PTH) mediated hypercalcemia.

Case presentation: We report a case of parathyroid carcinoma with a difficult histological diagnosis. This case illustrates the usefulness of the immunohistochemical marker "GATA-3" in parathyroid differentiation especially in tumours.

Clinical discussion: The diagnosis of parathyroid carcinoma is challenging without the knowledge of the clinical information, laboratory finding, and radiographic imaging studies. The immunohistochemistry is useful tool in these cases to identify the parathyroid origin of neoplasia. GATA-3 is a transcription factor that is involved in the embryonic development of the parathyroid glands and in adult parathyroid cell proliferation.

Conclusion: It is concluded that GATA-3 is a very sensitive and relatively specific immunohistochemical marker for parathyroid differentiation that can assist in the differential diagnosis of parathyroid tumours.

1. Introduction and Importance

Parathyroid carcinoma is a rare disease, defined as a malignant neoplasm originating from parathyroid parenchymal cells [1]. This carcinoma is often poorly differentiated and difficult to diagnose. Immunohistochemistry is crucial for diagnosis confirmation [2]. Below, we report a case of parathyroid carcinoma with a difficult histological diagnosis. We had follow the instruction of 2020 scare guidelines [3].

2. Case presentation

A 38-year-old women, without personal or family history, complained of bone pain. She didn't have drugs allergic or psychosocial history. Clinical examination revealed a right juxta thyroid nodule, suggesting a metastatic recurrential adenopathy. Laboratory exam found hypercalcemia, hypophosphoremia and an excess of PTH. The cervical nodule was excised and sent to our department of pathology for frozen section examination. The operation was undergone by a 20 years-experience professor without any complication. The patient left the hospital after 1 week.

In gross, the specimen was poorly circumscribed, measuring 3.5 cm and weighting 6g. On cut section, it was white and firm. The frozen section examination concluded to a malignant proliferation. Thereafter, a total thyroidectomy was performed, showing no macroscopic abnormalities.

After formalin fixation and paraffin embedding, the histopathological examination showed a malignant nodular proliferation (Fig. 1), composed of intermediated-size cells, with round to ovoid nuclei, containing dense and clumped chromatin, with macronucleoli (Fig. 2). Many atypical mitotic figures were present. The tumoral growth was subdivided by broad bands of fibrous connective tissue extending from the peritumoral capsule, which was invaded; as well as the muscle tissue around (Fig. 3). Vascular and perineural invasion was frequently observed too (Fig. 4). A poorly differentiated thyroid carcinoma, and medullary thyroid carcinoma were both evoked. On immunohistochemistry, the tumour cells were negative for thyroid transcription factor 1 (TTF-1), thyroglobulin, calcitonin and neuroendocrine markers,

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List of abbreviations

PTH	parathyroid hormone
HPF	high-power fields
TTF-1	thyroid transcription factor 1
IHC	immunohistochemistry

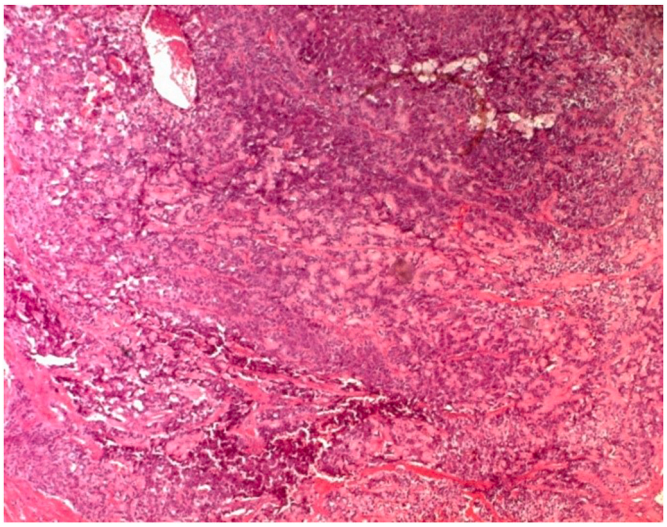

Fig. 1. Malignant nodular growth (HEx40).

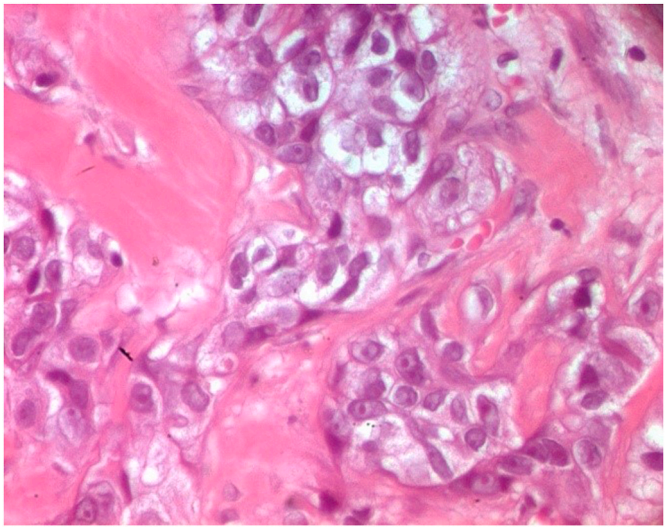

Fig. 2. Mildly to moderately pleomorphic chief cells with clear cytoplasm and macronucleoli (HE × 400).

eliminating so a thyroid medullary carcinoma, but not thyroid anaplastic carcinoma, since this tumour does not express TTF1.

Moreover, the thyroid tissue was of normal morphology. Considering biological data, a parathyroid malignancy was indeed suspected. So, we completed our immunohistochemical study with GATA-3: a marker expressed by parathyroid cells, and negative in thyroid tissue. The tumoral cells was strongly positive for this antibody (Fig. 5).

Thus, the clinical-pathological confrontation and above all, the results of the immuno-histochemical study enable us to conclude with a parathyroid carcinoma.

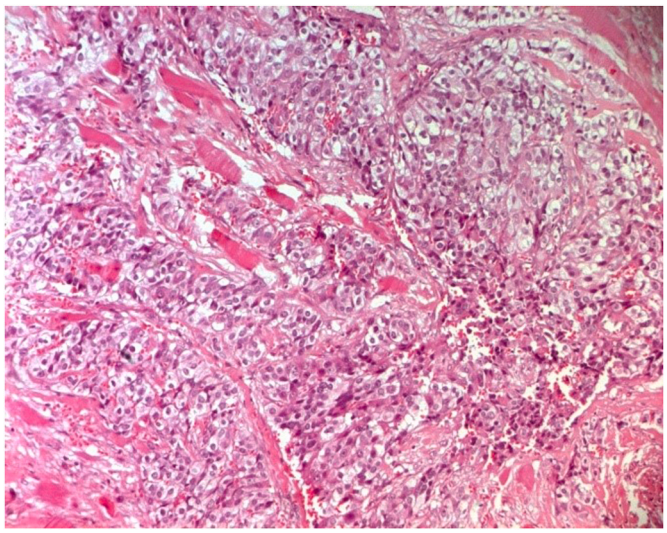

Fig. 3. Tumour cells invading muscle tissue (HE × 100).

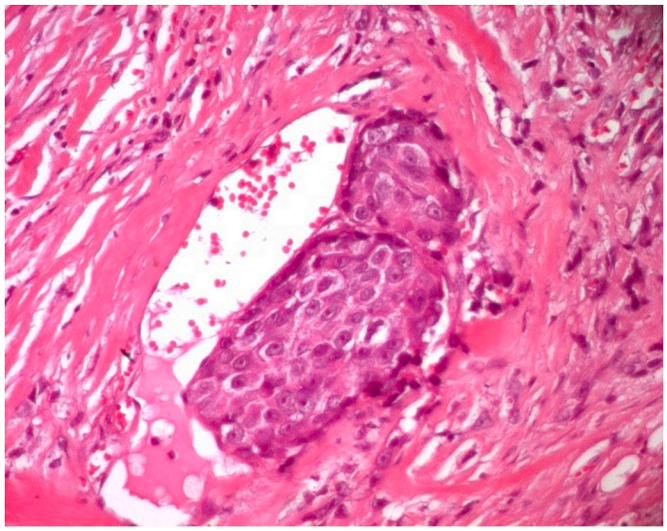

Fig. 4. Vascular invasion (HE × 200).

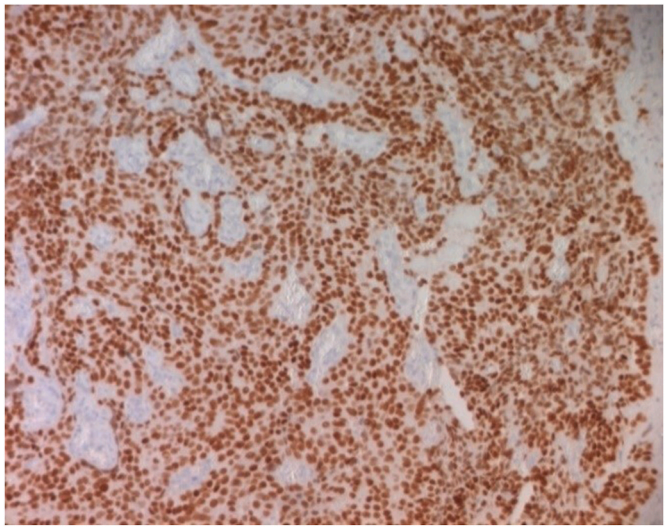

Fig. 5. Positive nuclear staining with GATA-3 (IHC × 200).

2.1. Clinical Discussion

Parathyroid carcinoma is exceptional, accounting less 1% of cases of primary hyperparathyroidism [2]. Most parathyroid carcinomas are sporadic, however, they have also been reported to occur in association with familial isolated hyperparathyroidism, familial hyperparathyroidism jaw tumour syndrome and after neck irradiation [2].

The sex-ratio is close to 1 and the mean patient age at diagnosis is 50 years [1]. The clinical presentation is variable, dominated by the effects of excess secretion of parathyroid hormone with calcium levels often >14 mg/dl, as in our case. The clinical manifestations include renal disease, often with nephrolithiasis, bone disease with osteitis, diffuse osteoporosis and fractures or both renal and bone disease [2]. Additional symptoms include those of hypercalcemia, such as fatigue, weakness, weight loss, anorexia, nausea, vomiting, polyuria, and polydipsia [2]. Similarly, to our case, a palpable neck mass is present in 15–75% of cases, depending on the series [2]. Parathyroid tumours usually occur at the posterior or near the lower pole of the thyroid, where the normal parathyroid tissue is located [1]. They can also arise in a variety of other sites within the neck, retro-oesophageal space, mediastinum and thymus. However, they may invade the thyroid and they may be interpreted as thyroid nodules by ultrasound examination [4].

Parathyroid carcinomas show considerable variation in their macroscopic features. They are typically solitary, large and variably encapsulated with an average diameter presentation of 3 cm and weight between 2 and 10 g [5]. Their colour is different from normal parathyroid glands and ranges from greyish to white [5]. These tumours are often solid with irregular margins and appear to be adherent or invading adjacent structures, such as the strap muscles, thyroid gland, recurrent laryngeal nerve, trachea, and oesophagus [5]. A total of 21% of parathyroid carcinoma may exhibit a cystic component, which could potentially be ruptured during intraoperative manipulation. It is, therefore, essential that careful tissue handling is exhibited [5].

The histological examination reveals a nodular and solid growth pattern. The tumour cells can be uniform or presenting a mild to moderate nuclear atypia. Parathyroid carcinomas are mostly composed of chief cells; however, oxyphil cells and transitional cells can also be seen. Increased mitotic activity (>5/50 HPF) and atypical mitosis may be seen. Necrosis and broad fibrous bands can be present. One of the following features is necessary for definitive malignancy diagnosis of parathyroid lesion: vascular invasion, perineural invasion, Invasion of adjacent structures or organs metastasis [2]. Almost of these features were observed in our case.

For pathologists, parathyroid tumour is a diagnostic challenge due to overlapping morphological features with thyroid lesions [6]. Many cases are misdiagnosed as follicular neoplasm of the thyroid [6].

Currently, the biomarkers for the parathyroid cells are PTH and chromogranin A. An *anti*-PTH antibody was shown to specifically react with parathyroid cells, but the sensitivity was not sufficiently high. PTH immunostaining is frequently weak or shows focal positivity, particularly in adenoma, carcinoma, and oxyphilic cells [4]. This anti-body wasn't used in our case, since it was not available in our department. Chromogranin A is not specific as it is also expressed in medullary carcinoma of the thyroid [4].

GATA-3 is a member of the GATA family of zinc finger transcription factors, and it is detected in human embryos from the beginning of the 4th gestation week [4]. It plays an important role in embryogenesis, development, and cell differentiation in many organs and tissues, including the kidney, breast, nervous system, thymocytes, T lymphocytes and hair follicles [4]. GATA-3 is also implicated in the embryonic development of the parathyroid glands, as well as in the proliferation of adult parathyroid cells [4]. Overall, these data strongly suggest that GATA-3 can be used as a specific immunohistochemical biomarker for parathyroid cells [4].

Our case and many series illustrate that the nuclear immunoreactivity for GATA-3 was revealed in all hyperplastic parathyroid glands, as well as parathyroid adenomas and carcinomas [4]; whereas, all thyroid tumours, renal cell carcinomas, thymic epithelial tumours, and carcinoid tumours investigated for comparison purposes were negative for this marker.

TTF-1 is a transcription factor expressed in thyroid and lung tissue. Its immunoreactivity is observed in 100% of thyroid follicular lesions, including goiter and follicular neoplasm, 96% of papillary thyroid carcinomas and in 90% of medullary carcinomas; however, this marker is usually negative in poorly and indifferenciated thyroid carcinoma [6].

In our case and in many recent series, it has been shown that GATA-3 expression is specific for the cells of parathyroid origin and it is more reliable than PTH or chromogranin A in distinguishing between parathyroid and thyroid lesions [6]. GATA-3 expression is detected also by immunohistochemistry in urothelial and breast carcinomas [4]. GATA-3 is also a highly reliable biomarker for detecting paraganglioma, pheochromocytoma, and neuroblastic tumours [4].

Molecular analysis is not indicated or approved to differentiate parathyroid vs thyroid lesions and is only performed on occasion when parathyroid lesions are misinterpreted as thyroid follicular neoplasms [6].

3. Conclusion

It is concluded that GATA-3 is a useful tool, that enable the distinction of parathyroid lesion from thyroid one, particularly in case of poorly differentiated carcinoma [7].

Consent of patient

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

Ethical approval

This study is exempt from ethical approval at our institution.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contributions

Ahlem Bdioui and Zainab Lajmi: analysed and interpreted the patient data, participate to the acquisition of data and was responsible for the conception and design.

Nabiha Missaoui, Ahlem Bchir, Emene Ben Ammou and Oussama Belkacem: participate to the interpretation of data.

Sihem Hmissa has drafted the work and revised it.

All authors read and approved the final manuscript.

Registration of research studies

1. Name of the registry: N/A*
2. Unique identifying number or registration ID:N/A*
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):N/A*

* Exempt, not a first case report.

Guarantor

Ahlem Bdioui.

Declaration of competing interest

The authors have no conflict of interest to disclose.

References

[1] C. Rodriguez, S. Nadéri, C. Hans, C. Badoual, Parathyroid carcinoma: a difficult histological diagnosis, Eur Ann Otorhinolaryngol Head Neck Dis 129 (2012) 157–159.
[2] C. Marcocci, F. Cetani, M.R. Rubin, S.J. Silverberg, A. Pinchera, J.P. Bilezikian, Parathyroid carcinoma, J. Bone Miner. Res. 23 (2008) 1869–1880.
[3] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, A. Kerwan, SCARE Group, The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int J Surg Lond Engl 84 (2020) 226–230.
[4] N. Takada, M. Hirokawa, A. Suzuki, M. Higuchi, S. Kuma, A. Miyauchi, Diagnostic value of GATA-3 in cytological identification of parathyroid tissues, Endocr. J. 63 (2016) 621–626.
[5] J. Goswamy, M. Lei, R. Simo, Parathyroid carcinoma, Curr. Opin. Otolaryngol. Head Neck Surg. 24 (2016) 155–162.
[6] Y. Shi, T.C. Brandler, M. Yee-Chang, et al., Application of GATA 3 and TTF-1 in differentiating parathyroid and thyroid nodules on cytology specimens, Diagn. Cytopathol. 48 (2020) 128–137.
[7] N.G. Ordóñez, Value of GATA3 immunostaining in the diagnosis of parathyroid tumors, Appl. Immunohistochem. Mol. Morphol. AIMM 22 (2014) 756–761.