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Case report

One case of so-called thyroid adenoma with bizarre nuclei that was reconfirmed as thyroid carcinoma based on the genetic mutation of the exon 5 of p 53 by Polymerase chain reaction-single strand conformational polymorphism (p 53-SSCP) of the formalin-fixed paraffin-embedded specimen

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Background: Generally the cytopathological atypism is considered to be one of diagnostic criteria of cancer. But it is thought that even benign tumors often show cellular atypism in endocrine tumors, which cannot be regarded as the malignant criterion. Among thyroid tumors of endocrine organ, however, the true biological malignancy of thyroid follicular adenoma with bizarre nuclei, alias atypical follicular adenoma of thyroid, has not been distinctly settled yet and this pathological diagnosis has been used with an uncertain malignant potentiality. We had an opportunity to study a case of follicular adenoma with nuclear atypism genetically and report its biological malignancy. Case: 30-year-old female patient revealed single expansive mass of 4 cm in diameter with multicystic and calcified configuration. An aspiration cytology revealed several aggregates of follicular cells with bizarre nuclei and multinucleated cells without any necrosis and dispersed single tumor cells. Anaplastic carcinoma of thyroid gland was cytopathologically suggested. Postoperative pathology indicated follicular adenoma with bizarre nuclei, mainly consisted of usual follicular adenoma without any atypism. On immunohistochemistry there was a slight increment of Ki-67-positive cells with no p 53-positive cells. Surrounding usual follicular tumor cells failed to be stained with above two reagents. In a genomic analysis of p 53 suppressor gene the mutation of exon 5 was detected in bizarre cells of adenoma, but not in the usual follicular adenoma and the normal control specimen. Conclusion: The genomic mutation of p 53 suppressor gene has been often seen in undifferentiated thyroid carcinoma or in the dedifferentiation progression of thyroid carcinoma. These observation made us speculate that some follicular adenomas with bizarre nuclei were minute de novo anaplastic carcinomas or borderline lesions between adenoma and anaplastic carcinoma.

Key words: thyroid adenoma with bizarre nuclei, atypical follicular adenoma of thyroid, polymerase chain reaction-single strand conformational polymorphism (SSCP), p 53-SSCP, formalin-fixed paraffin-embedded specimen, immunohistochemistry, Ki-67

Case report

30-year-old female patient revealed single expansive mass of 4 cm in diameter with multicystic and calcified configuration. An aspiration cytology revealed several aggregates of follicular cells with bizarre nuclei and multinucleated cells without any necrosis and dispersed single tumor cells (Fig. 1). Anaplastic carcinoma of thyroid gland was cytopathologically suggested. A hemilobectomy was performed. Postoperative pathology indicated follicular adenoma with bizarre nuclei, mainly consisted of usual follicular adenoma without any atypism (Fig. 2). Immunohistochemically only several follicular cells with bizarre nuclei were stained with anti-Ki-67 antibody regardless of their atypism, less than 5%, but there was no positive cells in p 53 investigation (Fig. 3). There was no infiltration nor metastasis. In a genomic analysis of p 53 suppressor gene deoxyribonucleic acid (DNA) was extracted from the trimmed focus consisted of cells with bizarre nuclei in routinely processed formalin-fixed paraffin-embedded tissue specimen. p 53-SSCP was performed according to our previously reported method (2-4). The mutation of exon 5 was detected as an additional band in bizarre cells of adenoma, but not in the usual follicular adenoma and the normal control specimen (Fig. 4). There was no mutations in other exons, including exon 6, 7, and 8.

Discussion

p 53 is one of the suppressor genes, which prevent an oncogenesis. So the oncogenesis is promoted by the abortive genomic mutation of suppressors against tumorigenesis. This type of p 53 genomic mutation has been reported in the process of carcinoma of both poorly or anaplastic differentiation and metastatic potentiality (Fig. 5) (1, 5). The mutation of exon 5 of p 53 was revealed within the specified cells with cellular atypism in our follicular adenoma with bizarre nuclei by p 53-SSCP study.

This genetic mutation of p 53 was also reported (1). These p 53 genomic defects suggested that the cells with atypism in follicular adenoma with bizarre nuclei were anaplastic carcinoma of early phase, namely, follicular adenoma with bizarre nuclei consisted of both usual adenoma and minute anaplastic carcinoma. It was useful to recognize the aggressive carcinoma at the early stage for preventing from life−threatening. On immunohistochemistry there was no overproduction of defective p 53−products.

Because there were still variations of cellular atypism among cases and previous reports consisted of only case reports, the biological malignancy of this tumor remained to be established. It is necessary to analyze its malignancy by the genomic study with p 53−SSCP in all cases.

Acknowledgement

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和 文 抄 録

ホルマリン固定―パラフィン包埋材料を使った遺伝子検査上 p 53−SSCP 変異を同定し、甲状腺癌が示唆された巨大核を伴う甲状腺腺腫の一症例

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背景：通常、細胞病理学的異型性は、がんの病理学的診断基準のうちの 1 つであると考えられる。しかし、内分泌臓器の腫瘍に関しては、良性腫瘍でさえしばしば高度な細胞異型を示すとされ、細胞異型性は悪性基準とならない。内分泌臓器としての甲状腺の腫瘍において、奇怪な核異型を伴う甲状腺濾胞性腺腫（別名、異型濾胞性甲状腺腺腫）の真実の生物学的悪性度は未だ明確となっておらず、この病理診断名が不確かな悪性度のまま日常臨床で使用されている。今回、我々は、奇怪な核異型を伴う甲状腺濾胞性腺腫の遺伝病理学的検査を実施し、その生物学的悪性度を検討する機会を得たので、報告する。症例：症例は 30 才の女性で、単発性で、多嚢胞性の直径 4 cm の圧排限局性腫瘤であった。腫瘍穿刺細胞学的所見上、壊死を欠如した、散在性の奇怪な核と多核細胞を伴う濾胞性腫瘍細胞集簇が認められ、甲状腺の未分化癌が示唆された。手術後の摘出物の病理組織学的検討上、奇怪な核を伴う濾胞性腺腫と診断されたが、細胞異型性を欠如した通常の濾胞性腺腫が主体であった。免疫組織化学的検査上、細胞異型の高度な腫瘍細胞は p 53 陰性で、Ki−67 陽性細胞が散在性に少数認められた。周囲の濾胞性腺腫細胞は両者とも陰性であった。p 53 抑制遺伝子の遺伝子分析において、通常の濾胞性腺腫部分と正常対象組織では遺伝子変異は認められず、奇怪な核異型を伴う甲状腺濾胞性腺腫の細胞異型部分においてのみエクソン 5 の遺伝子変異が認められた。結論：p 53 抑制遺伝子の変異は、甲状腺の未分化がんまたは甲状腺がんの退形成に伴ってしばしば認められる。このことは、我々を奇怪な核を伴う濾胞性腺腫は、良性の腺腫と未分化がんの中間群、または、de novo に発生した未分化がんの早期がんであると推定された。

キーワード：巨大核を伴う甲状腺腺腫、異型濾胞性甲状腺腺腫、p 53−SSCP、ホルマリン固定―パラフィン包埋材料、免疫組織化学、Ki−67

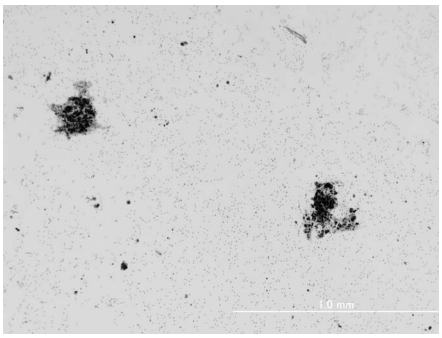
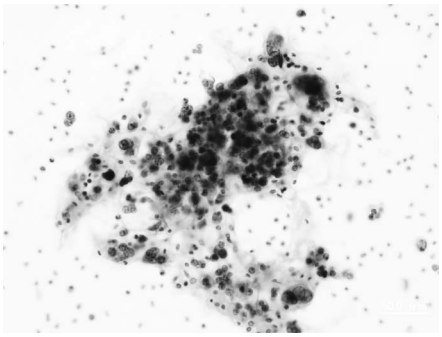


Fig. 1 a



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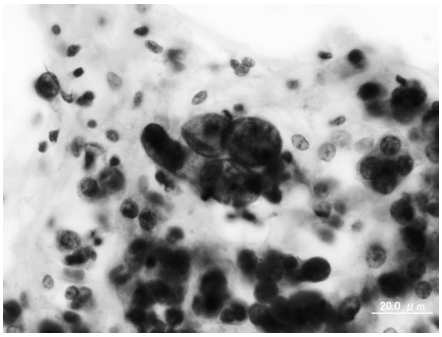

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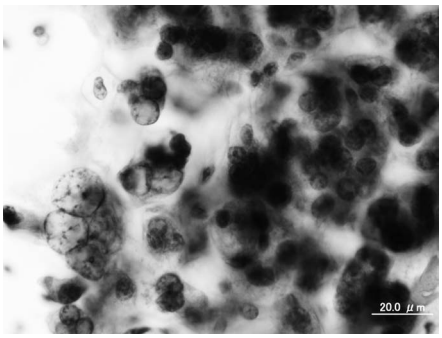

Fig. 1 d

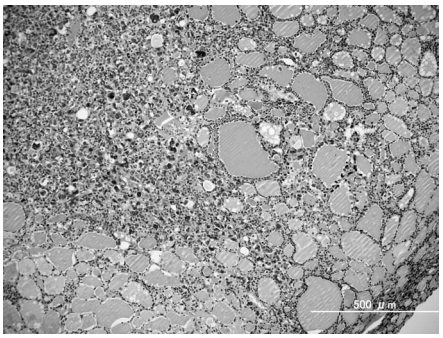

Fig. 2 a

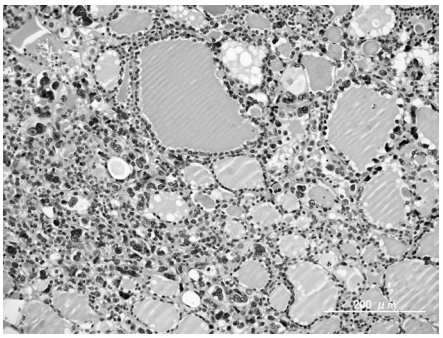

Fig. 2 b

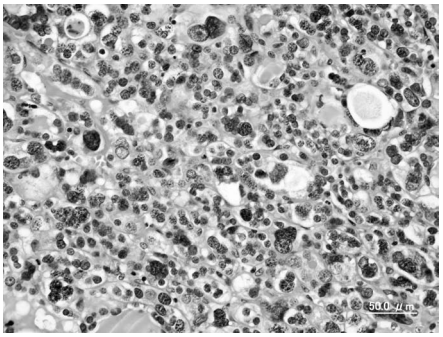

Fig. 2 c

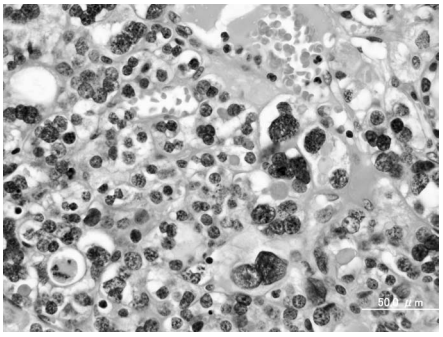

Fig. 2 d

One case of so－called thyroid adenoma with bizarre nuclei that was reconfirmed as thyroid carcinoma based on the genetic mutation of the exon 5 of p 53 by Polymerase chain reaction－single strand conformational polymorphism (p 53－SSCP) of the formalin－fixed paraffin－embedded specimen

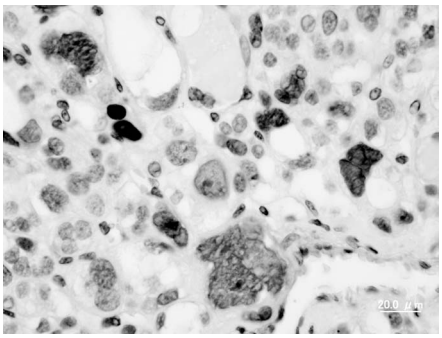

Fig. 3 a

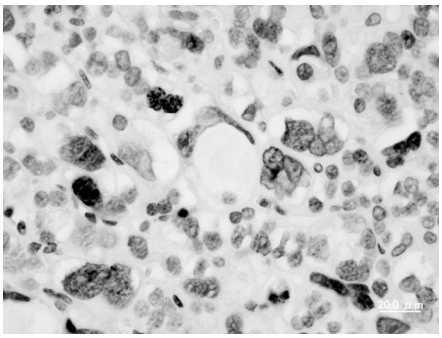

Fig. 3 b

Fig. 3 c. Immunohistochemical results

cytopathology		p 53	Ki－67
follicular adenoma	without any atypism	－	－
	with bizarre nuclei	－	＋（＜5％）

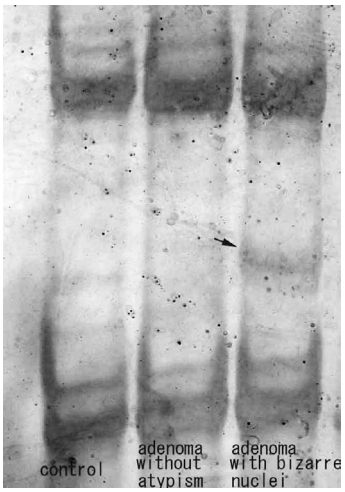

Fig. 4

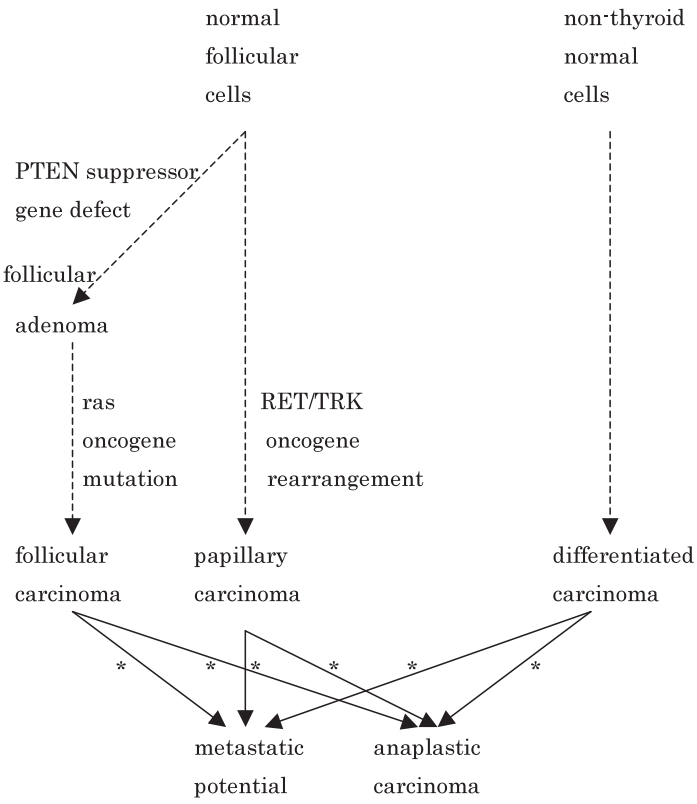

Fig. 5. Mutation of suppressor gene p 53 was found in various processes of carcinomas *