Case Report
Squamous cell carcinoma of the lung with highly proliferating fibromatosis-like stroma: a rare phenomenon

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Abstract: Few cases of carcinoma with exuberant stromal proliferation have been documented, apart from scirrhous carcinoma. To the best of our knowledge, previous cases of carcinoma exhibiting exuberant stromal proliferation have exclusively been reported in the thyroid gland, specifically as papillary carcinoma. The exuberant stromal proliferation has been recognized to be similar to either fibromatosis or nodular fasciitis. Herein, we report a case of a 74-year-old Japanese man whose tumor in the upper lobe of his right lung displayed highly proliferating stroma with dispersed, poorly differentiated squamous cell carcinoma nests. The stromal spindle cells (fibroblasts/myofibroblasts) had similar molecular profiles to those typically observed in fibromatosis rather than nodular fasciitis, resulting in the designation of "fibromatosis-like" stroma. The presence of carcinoma cells, along with stromal cells, expressing TGF-β in this case likely fostered continuous stromal proliferation, presumably in conjunction with the unique microenvironment in which the carcinoma cells were present.

Keywords: Fibromatosis, lung, squamous cell carcinoma, TGF-β

Introduction

Few cases of carcinoma, apart from scirrhous carcinoma, have shown exuberant stromal proliferation, which is similar to either fibromatosis or nodular fasciitis. To the best of our knowledge, such cases have been exclusively reported in the thyroid gland, and among the types of thyroid carcinoma, papillary carcinoma is typically accompanied by such a stroma [1, 2]. Stromal elements account for 60-80% of tumors [2]. Cases of papillary carcinoma have been reported as papillary thyroid carcinoma with nodular fasciitis-like stroma or as papillary thyroid carcinoma with fibromatosis-like stroma [1, 2], with some authors opposing both of these terms and proposing the term 'papillary carcinoma of the thyroid gland forming myofibroblastic nodular tumors' [1, 3]. The opposing opinion derives from the necessity that a mass formation caused by this type of stroma is emphasized, in contrast to a mere prominent stromal reaction [1, 3].

Herein, we report of a 74-year-old Japanese man whose tumor in the upper lobe of his right lung displayed highly proliferating stroma with dispersed, poorly differentiated squamous cell carcinoma (SCC) nests. Although mass formation due to stromal overgrowth was observed in our case, we present this case as a carcinoma-associated stromal overreaction without putting as much emphasis on the mass-forming morphology of the stroma, especially when considering the term that better implicates the molecular mechanism for the development of such a stroma.

Clinical Summary

A 74-year-old Japanese man without a significant medical history was referred to our hospital with an abnormality on his chest radiograph discovered during his regular examination. Chest computed tomography (CT) revealed a mass lesion that measured 31 × 28 × 26 mm in the right upper lobe and another mass lesion
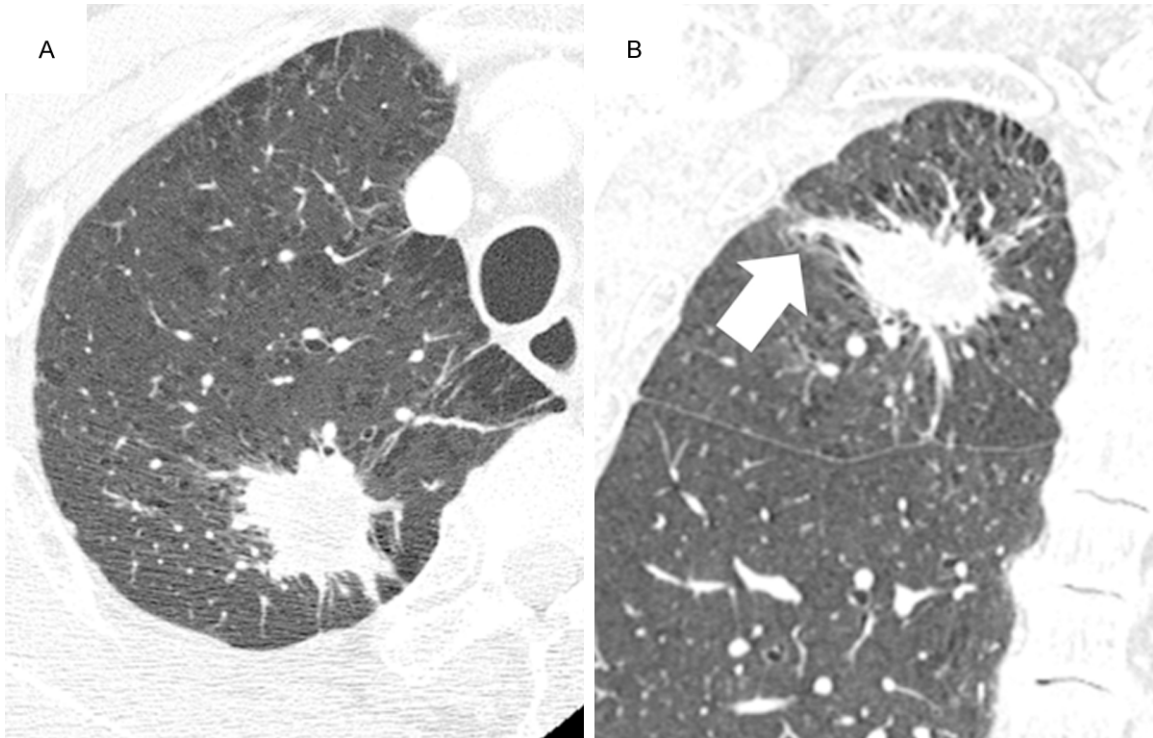
Figure 1. Computed tomography scan. Axial (A) and coronal (B) images of the chest computed tomograph show a mass lesion, 31 × 28 × 26 mm, with prominent, coarse spiculations along its margin in the right upper lobe. The longest spiculation (arrow) is 20 mm with a maximum width of 5 mm.
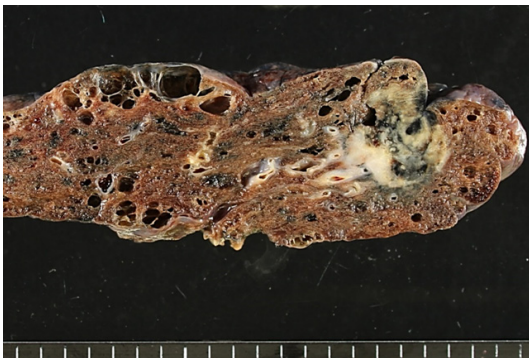

Figure 2. Gross findings of the surgically resected specimen of the right upper lobe. The tumor is whitish-to-tan colored with anthracotic discoloration. Pleural indentation is observed.

measuring 18 × 16 × 15 mm in the right middle lobe; no significant lymph node swelling or distant metastasis was detected. The mass lesion in the right upper lobe showed prominent coarse spiculations along its margin; the spiculations were more accentuated than those typically observed in lung cancer (**Figure 1A**, **1B**). Although the mass in the right upper lobe was difficult to diagnose using bronchoscopy and bronchial scraping cytology, the mass in the right middle lobe was diagnosed as adenocarcinoma through bronchial scraping cytology. Subsequently, surgery was performed. Since an intraoperative histopathological examination of the spiculated mass in the right upper lobe revealed carcinoma, a right upper and middle lobectomy was performed. The patient's post-operative course was uneventful, and he was discharged from the hospital.

Pathological Findings

The surgically resected specimen of the right upper lobe revealed a whitish-to-tan-colored tumor with anthracotic discoloration. Pleural indentation was observed (**Figure 2**). The specimen from the right middle lobe also exhibited a whitish tumor with anthracotic discoloration.

Histopathological examination of the tumor in the right upper lobe revealed tumor cells immersed in a highly proliferating stroma that was mainly composed of fibroblasts/myofibroblasts and collagen fibers (**Figure 3A**). Tumor
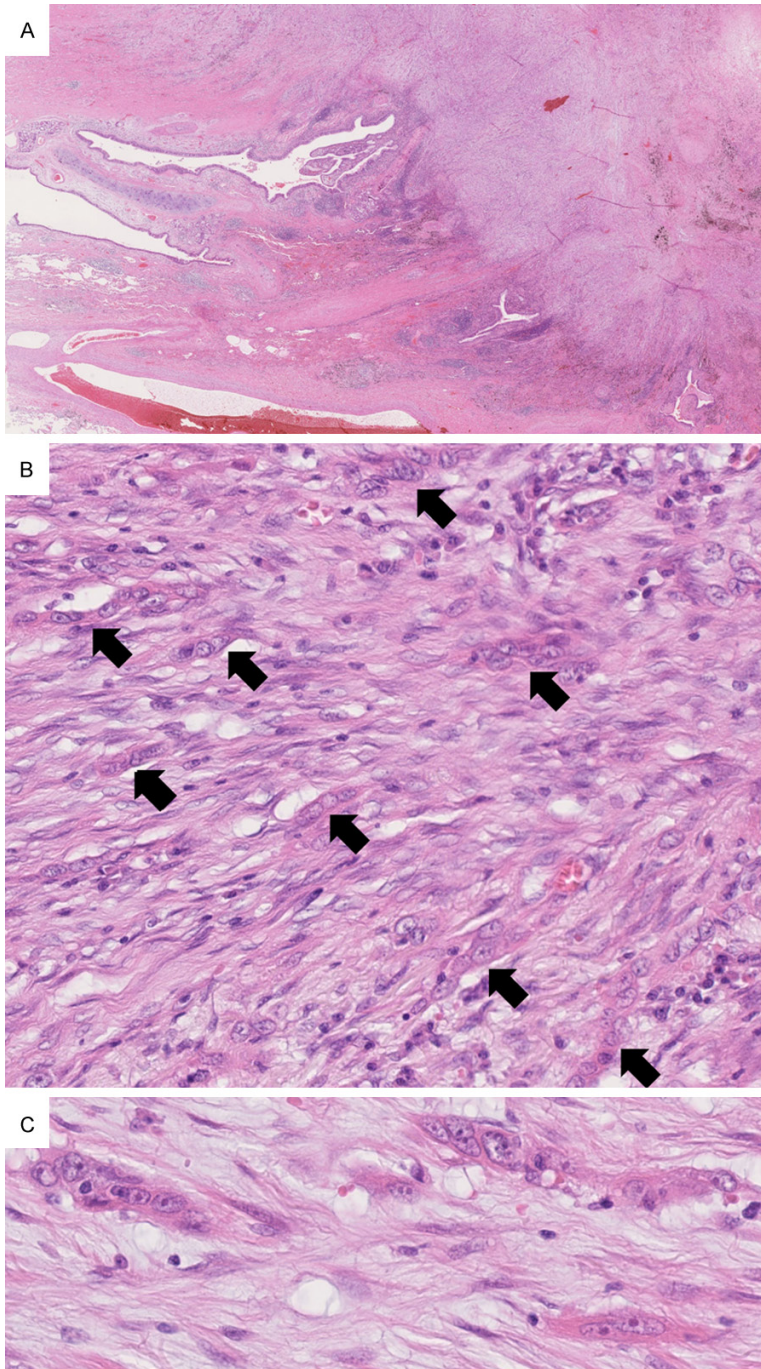
Figure 3. Microscopic findings of the tumor in the right upper lobe. A. The tumor cells are immersed in a highly proliferating stroma that is mainly composed of fibroblasts/myofibroblasts and collagen fibers (12.5 ×). B. The tumor cells (arrows) show a trabecular nest and infiltrated streaming in line with the arrangement of the spindle cells (fibroblasts/myofibroblasts) and collagen fibers; no gland formation or keratinization were observed (200 ×). C. The nuclei of the tumor cells are enlarged with prominent nucleoli; proliferating stromal cells do not show atypia (600 ×).

cells showed a trabecular nest and infiltrated streaming in line with the arrangement of the

spindle cells (fibroblasts/myofibroblasts) and collagen fibers; no gland formation or keratinization were observed (**Figure 3B**). The nuclei of tumor cells were enlarged, and the nucleoli were prominent; proliferating stromal cells did not show atypia (**Figure 3C**). Scarred tissue was not apparent in the stroma. The stroma occupied approximately 80% of the tumoral mass. In contrast, the tumor in the right middle lobe was a typical adenocarcinoma. Lymphatic invasion, vascular invasion, pleural invasion, and lymph node metastasis were not apparent in either tumor. The tumor in the right upper lobe was staged as pT2aN0, and the tumor in the right middle lobe was staged as pT1aN0. The surgical margins of both tumors were tumor-free.

Upon immunohistochemical analysis, the tumor cells in the right upper lobe showed expression of CK5/6 (D5/16 B4, 1:100; Dako, Glostrup, Denmark) (**Figure 4A**) and p40 (polyclonal, 1:500; Nichi-rei Biosciences, Tokyo, Japan) (**Figure 4B**). TTF-1 (8G7G3/1, 1:100; Dako) and Napsin A (IP64, 1:100; Novocastra, Newcastle Upon Tyne, UK) were not expressed in the tumor cells. Some of the stromal spindle cells were positive for αSMA (1A4, 1:50; Dako) (**Figure 4C**), which was consistent with a mixed-cell population of myofibroblasts and fibroblasts. Transforming growth factor-β (TGF-β; 1D11, 1:100; R&D Systems, Minneapolis, MN) was expressed in both tumor cells and stromal spindle cells (**Figure 4D**). Nuclear/cytoplasmic accumulation of β-catenin (β-Catenin-1, 1:100;
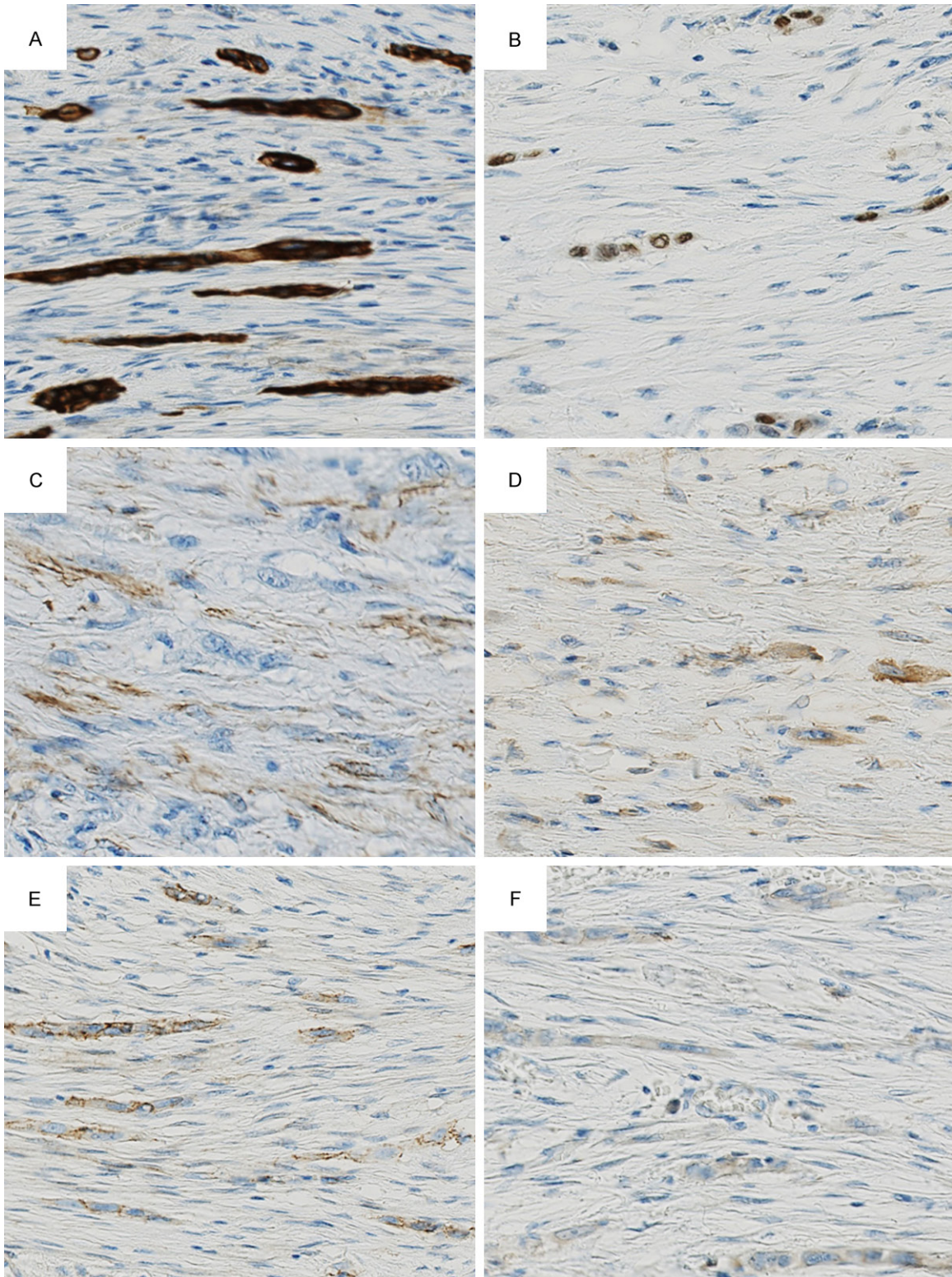
Figure 4. Immunohistochemical findings of the tumor in the right upper lobe. A. The tumor cells showing CK5/6 expression (400 ×). B. The tumor cells showing p40 expression (400 ×). C. Some stromal spindle cells are positive for αSMA (400 ×). D. TGF-β is immunostained in both tumor cells and stromal spindle cells (400 ×). E. Nuclear/cytoplasmic accumulation of β-catenin is not observed in stromal spindle cells. Of note, the cellular membranes of the tumor cells are positive for β-catenin (400 ×). F. MMP9 is faintly expressed in tumor cells but not in stromal spindle cells (400 ×).

Dako) was not observed in stromal spindle cells; however, the cellular membranes of the tumor cells were positive for β-catenin (**Figure 4E**). Matrix metalloproteinase 9 (MMP9; EP1254, 1:100; Epitomics, San Francisco, CA) was faintly expressed in tumor cells but not in stromal spindle cells (**Figure 4F**).

A diagnosis of poorly differentiated SCC was rendered for the right upper lobe tumor. Its highly proliferating stroma was recognized not as nodular fasciitis-like, but fibromatosis-like, in spite of a lack of nuclear/cytoplasmic accumulation of β-catenin; spindle cells expressing TGF-β but not expressing MMP9 were similar to those typically observed in fibromatosis.

Discussion

SCC of the lung can be classified as either the central type or the peripheral type according to its primary site. It was reported that the peripheral type accounts for approximately 50% of SCC [4]. A certain percentage of the peripheral type is known to have a spiculated margin similar to that observed in adenocarcinoma, which more commonly exhibits spiculation than SCC [5]. The spiculation seen in adenocarcinoma histologically corresponds to strands of fibrous tissue, to direct infiltration of the tumor into the adjacent parenchyma, or to the spread of the tumor in the lymphatic channels and interstitial tissue of adjacent vessels, airways, or interlobular septa [5]. Spiculation with histological origins, as mentioned above, is commonly observed as fine structures in CT. On the other hand, spiculation observed in our case is coarser than usual, with the longest one measuring 20 mm in length with a maximum width of 5 mm; this finding is probably caused by a highly proliferating fibromatosis-like stroma.

It is necessary to differentiate between reactive and neoplastic conditions regarding stromal cell proliferation. As the stromal cells did not show apparent atypia, they would not have a malignant nature. As for whether their proliferation is neoplastic or not, it would not be neoplastic, even though the proliferation of the stromal cells exceeded the limit of usual stromal reactions observed in carcinoma. To speculate about the mechanism underlying the exuberant stromal proliferation, it has been demonstrated that papillary carcinoma causing stromal overgrowth, as well as scirrhous gastric

carcinoma, express TGF-β, suggesting that TGF-β may promote this phenomenon [2, 6-8]. It has also been shown that carcinoma cell-derived TGF-β modulates myofibroblast differentiation in SCC [9]. TGF-β increases myofibroblasts within the carcinoma microenvironment and enhances extracellular matrix (ECM) synthesis while inhibiting ECM degradation at the same time [10-12]. ECM synthesis is also promoted by TGF-β secreted from stromal cells [13], and TGF-β expression in stromal cells was found in our case and in another case of papillary carcinoma by immunohistochemistry [2]. As TGF-β receptors were immunostained in the stromal cells adjacent to carcinoma cells [14], it was postulated that TGF-β, acting in an autocrine/paracrine manner in the stromal cells, is important for the synthesis of ECM, as is the function of carcinoma-secreting TGF-β [13]. Proliferating stromal cells (fibroblasts/myofibroblasts) stimulated by TGF-β produce collagen; this reaction subsides as the collagen is increasingly deposited in the matrix [12, 14, 15]. Our case and other cases of papillary carcinoma with stromal overgrowth did not exhibit a significant amount of scarred tissue. It is thus supposed that the persistence of early phase stromal reactions for carcinomas is associated with the exuberant proliferation of stromal cells in such cases. For stromal overgrowth to continue, the capacity for maturation to scarred tissue formation should be limited in order to maintain an early-phase phenotype in the stromal cells; the tendency to form scarred tissue was not obvious in our case or in other cases of papillary carcinoma with stromal overgrowth.

As metastatic foci of papillary carcinoma with stromal overgrowth did not form similar stroma to the primary site [1], the differences in the microenvironments between the primary and metastatic foci might be responsible for permitting the persistent early-phase phenotype of the stromal cells in the primary site. This could explain why, to date, cases of carcinoma, except for scirrhous carcinoma, have shown stromal overgrowth exclusively in the thyroid gland; the thyroid microenvironment is probably important for this phenomenon to occur. The carcinoma in our case might not only express TGF-β but also exist in a unique microenvironment in the lung, where such a stromal reaction was initiated by chance.

The term 'fibromatosis-like' was applied to describe the nature of the stroma in this case. Stated as such, whether the actual nature of the stroma is more similar to fibromatosis or nodular fasciitis should be well examined, as they often display overlapping histopathological features [2]. To differentiate between fibromatosis and nodular fasciitis, analysis of the expression of β-catenin, TGF-β, Smad, several types of chemokine ligands, and MMPs plays an important role [16, 17]. First, β-catenin is often expressed at least focally in deep and superficial fibromatoses, with the former showing more diffuse and stronger nuclear expression than the latter [17, 18]. While deep fibromatosis usually exhibits mutation of the *CTNNB1* or *APC* genes [19, 20], superficial fibromatosis does not have mutations in the *CTNNB1* or *APC* genes [18]. Although nuclear β-catenin expression was not observed in the stromal cells in our case, it is acceptable to designate this case as fibromatosis-like stroma since some cases of superficial fibromatosis do not show nuclear expression of β-catenin [17, 18]. Second, the distinction between fibromatosis, particularly deep fibromatosis, and nodular fasciitis lies among the genes associated with inflammation and ECM remodeling. Deep fibromatosis shows increased expression of genes encoding molecules of the TGF-β signaling pathway [16], whereas nodular fasciitis displays elevated expression of genes encoding proteases participating in ECM degradation, such as MMP1, 3, 9, and 13 [16]. In our case, the stromal cells expressed TGF-β and did not express MMP9, which is consistent with the expression pattern of deep fibromatosis. Although nuclear β-catenin expression was not observed, TGF-β expression and the absence of MMP9 expression in the stromal cells were sufficient to designate the stroma in our case as 'fibromatosis-like'.

In conclusion, we have described an exceedingly rare case of SCC with a highly proliferating fibromatosis-like stroma. This unusual stroma was associated with coarse spicules on CT. The molecular profiles of the stromal cells were more similar to those of fibromatosis than of nodular fasciitis, which formed the basis of the designation of 'fibromatosis-like' stroma. The presence of carcinoma cells expressing TGF-β, as well as stromal cells expressing it, in this case likely fostered continuous stromal proliferation in conjunction with other factors in the microenvironment in which the carcinoma cells were present.

Disclosure of conflict of interest

None.

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References

[1] Naganuma H, Iwama N, Nakamura Y, Ohtani N, Ohtani H, Takaya K and Sakai N. Papillary carcinoma of the thyroid gland forming a myofibroblastic nodular tumor: report of two cases and review of the literature. Pathol Int 2002; 52: 54-58.

[2] Na KY, Kim HS, Sung JY, Park WS and Kim YW. Papillary Carcinoma of the Thyroid Gland with Nodular Fasciitis-like Stroma. Korean J Pathol 2013; 47: 167-171.

[3] Terayama K, Toda S, Yonemitsu N, Koike N and Sugihara H. Papillary carcinoma of the thyroid with exuberant nodular fasciitis-like stroma. Virchows Arch 1997; 431: 291-295.

[4] Funai K, Yokose T, Ishii G, Araki K, Yoshida J, Nishimura M, Nagai K, Nishiwaki Y and Ochiai A. Clinicopathologic characteristics of peripheral squamous cell carcinoma of the lung. Am J Surg Pathol 2003; 27: 978-984.

[5] Lee KS, Franquet T, Han J and Johkoh T. Muller's Diseases of the Lung: Radiologic and Pathologic Correlations. Baltimore, Philadelphia: Lippincott Williams & Wilkins; 2012.

[6] Toti P, Tanganelli P, Schurfeld K, Stumpo M, Barbagli L, Vatti R and Luzi P. Scarring in papillary carcinoma of the thyroid: report of two new cases with exuberant nodular fasciitis-like stroma. Histopathology 1999; 35: 418-422.

[7] Kinugasa S, Abe S, Tachibana M, Hishikawa Y, Yoshimura H, Monden N, Dhar DK, Nagasue N and Nagaoka S. Overexpression of transforming growth factor-beta1 in scirrhous carcinoma of the stomach correlates with decreased survival. Oncology 1998; 55: 582-587.

[8] Yoshida K, Yokozaki H, Niimoto M, Ito H, Ito M and Tahara E. Expression of TGF-beta and procollagen type I and type III in human gastric carcinomas. Int J Cancer 1989; 44: 394-398.

[9] Lewis MP, Lygoe KA, Nystrom ML, Anderson WP, Speight PM, Marshall JF and Thomas GJ. Tumour-derived TGF-beta1 modulates myofibroblast differentiation and promotes HGF/SF-dependent invasion of squamous carcinoma cells. Br J Cancer 2004; 90: 822-832.

[10] Siegel PM and Massague J. Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. Nat Rev Cancer 2003; 3: 807-821.

[11] Desmouliere A, Geinoz A, Gabbiani F and Gabbiani G. Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts. J Cell Biol 1993; 122: 103-111.

[12] Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C and Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 2002; 3: 349-363.

[13] Mizoi T, Ohtani H, Miyazono K, Miyazawa M, Matsuno S and Nagura H. Immunoelectron microscopic localization of transforming growth factor beta 1 and latent transforming growth factor beta 1 binding protein in human gastrointestinal carcinomas: qualitative difference between cancer cells and stromal cells. Cancer Res 1993; 53: 183-190.

[14] Faiz Kabir Uddin Ahmed A, Ohtani H, Nio M, Funaki N, Iwami D, Kumagai S, Sato E, Nagura H and Ohi R. In situ expression of fibrogenic growth factors and their receptors in biliary atresia: comparison between early and late stages. J Pathol 2000; 192: 73-80.

[15] Terui T, Niitsu Y, Mahara K, Fujisaki Y, Urushizaki Y, Mogi Y, Kohgo Y, Watanabe N, Ogura M and Saito H. The production of transforming growth factor-beta in acute megakaryoblastic leukemia and its possible implications in myelofibrosis. Blood 1990; 75: 1540-1548.

[16] Bacac M, Migliavacca E, Stehle JC, McKee T, Delorenzi M, Coindre JM, Guillou L and Stamenkovic I. A gene expression signature that distinguishes desmoid tumours from nodular fasciitis. J Pathol 2006; 208: 543-553.

[17] Carlson JW and Fletcher CD. Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature. Histopathology 2007; 51: 509-514.

[18] Montgomery E, Lee JH, Abraham SC and Wu TT. Superficial fibromatoses are genetically distinct from deep fibromatoses. Mod Pathol 2001; 14: 695-701.

[19] van Broekhoven DL, Verhoef C, Grunhagen DJ, van Gorp JM, den Bakker MA, Hinrichs JW, de Voijs CM and van Dalen T. Prognostic Value of CTNNB1 Gene Mutation in Primary Sporadic Aggressive Fibromatosis. Ann Surg Oncol 2015; 22: 1464-70.

[20] Scott RJ, Froggatt NJ, Trembath RC, Evans DG, Hodgson SV and Maher ER. Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3'APC gene mutation. Hum Mol Genet 1996; 5: 1921-1924.