Case Report

A Case of Nodular Pseudoangiomatous Stromal Hyperplasia (PASH)

Kae Okoshi*1, Hiroki Ogawa*2, Hirofumi Suwa*2, Tatsuyoshi Saiga*3, and Hisato Kobayashi*4

*1Department of Surgery, Graduate School of Medicine, Kyoto University, **2Department of Surgery, ***3Department of Pathology, and ****4Department of Radiology, Otsu Red Cross Hospital, Japan.

Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a common microscopic lesion that is found at breast biopsy, and presents with proliferation of the stromal cells and slit-like pseudovascular spaces with endothelial-like spindle cells. In contrast, nodular PASH is relatively rare. We report here a case of nodular PASH with multiple palpable masses.

A 49-year-old woman who had experienced gradual enlargement of her breasts for 13 years noticed an elastic but firm palpable mass in her breast. We were able to detect 7 masses in her right breast and 2 in the left. Ultrasonography and mammography demonstrated nonspecific findings, and FNA and CNB did not establish a diagnosis. An excisional biopsy was performed, and the pathological findings revealed nodular PASH. Eighteen months after the excisional biopsy, the size of the nodules and the whole breast had decreased remarkably. While the possibility of a change in the hormonal background or the influence of drugs was considered, we were not able to reach a single specific conclusion regarding the pathogenesis.


Key words: Pseudoangiomatous stromal hyperplasia (PASH), Breast tumor, Myofibroblast

Pseudoangiomatous stromal hyperplasia (PASH), which was first reported in 19861, is a type of benign proliferative lesion of the breast stroma that is characterized by slit-like pseudovascular spaces lined by endothelial-like spindle cells in keloid fibrosis1,2. PASH is often accompanied by other benign and malignant breast lesions3, although it is relatively rare for PASH to form a palpable nodule. It is generally considered that hormones, especially progesterone, can contribute to the formation of PASH. We report here a case in which breast enlargement and palpable nodules including PASH shrunk naturally, 18 months after excisional biopsy.

Reprint requests to Kae Okoshi, Department of Surgery, Graduate School of Medicine, Kyoto University, 54-Shogoin Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: kae_md@kuhp.kyoto-u.ac.jp

Abbreviations:
PASH, Pseudoangiomatous stromal hyperplasia; US, Ultrasonography; MMG, Mammography; FNA, Fine needle aspiration; CNB, Core needle biopsy; CT, Computed tomography; MRI, Magnetic resonance imaging; CD, Cluster of differentiation; SMA, Smooth muscle actin

Received October 12, 2005; accepted May 8, 2006

Case Report

A 36-year-old woman noticed slow, progressive enlargement of her breasts (the right was larger than the left) in 1990. After she detected soft nodules in her right breast, she visited a local hospital in March 2003. She underwent mammography (MMG), ultrasonography (US), computed tomography (CT), fine needle aspiration (FNA) and core needle biopsy (CNB). FNA was not useful because of low cellularity, and CNB performed twice demonstrated fibrotic proliferation, suggestive of phyllodes tumors. She was subsequently referred to our hospital. Seven nodules almost completely occupied the right breast and peau-de-orange changes of the skin were observed in the lower inner portion. There were two nodules in the left breast (Fig 1A, B). The nodules were firm, elastic and well-defined. The right breast was obviously larger than the left (Fig 1A). MMG showed no distinct tumor shadow because the breasts were large and firm with some nodules and sufficient pressure could not be applied. US demonstrated seven tumors in the right and two in the left breast, which had regular borders for the most part and showed low but partly heterogeneous echo-
genicity. In October 2003 an excisional biopsy was performed on a mass in the upper inner quadrant of her right breast to confirm the histological diagnosis (Fig 1B). The specimen was a well-circumscribed yellow-gray tumor, 3.8 × 3.0 × 1.9 cm in size.

She underwent MRI examination to investigate the residual masses. The MRI showed several high-intensity lesions on fat-suppressed T2-weighted images, and these lesions exhibited some septae with surrounding low-intensity signals (Fig 2). Furthermore, the time-intensity curves showed gradual increase, which suggested that the tumors were benign.

In April 2005, the size of both breasts and the remaining tumors had decreased remarkably, and the two nodules in the left breast were no longer palpable.

**Pathological Findings**

Initially, fibrocystic disease of the mammary glands with stromal hyperplasia was diagnosed. The epithelial proliferation included cystic dilatation of the ducts with apocrine metaplasia, blunt duct adenosis, and duct papillomatosis (Fig 3A). The diagnosis was determined by noting the proliferative epithelial changes. After some discussion, PASH was subsequently diagnosed. The vascular endothelial-like spindle cells formed a vessel-like slit in the stroma (Fig 3B) and immunohistochemical staining for CD34, CD31, D2-40, smooth muscle actin (SMA) and Factor VIII supported this diagnosis. The spindle cells were positive for CD34 and, in part, SMA (Fig 3C, D) and negative for CD31, D2-40 and Factor VIII. The slits were therefore neither true lymph nor blood vessels and were covered with myofibroblasts. The nuclei of the ductal epithelial cells were immunopositive for both estrogen and progesterone receptor, whereas the stromal cells were negative.

**Discussion**

Pseudoangiomatous stromal hyperplasia (PASH), which was first reported by Vuitch et al. in 1986, is a benign proliferative lesion of the breast stroma. Although the vascular endothelial-like spindle cells form vessel-like slits in the stroma, they are not true vessels covered with endothelia, but rather vacant spaces bordered with myofibroblasts. PASH can be accompanied by other types
of breast tumors. Ibrahim et al.\textsuperscript{9} reported that PASH could be detected microscopically (at least one lesion) in 23% of 200 cases of benign and malignant breast tumors. Morita et al.\textsuperscript{6} described that PASH was associated with mastopathy (14.1%), fibroadenoma (0.9%), and carcinoma (6.7%). On the other hand, nodular PASH is relatively rare. The histopathological differentiation between PASH and a low-grade angiosarcoma is important. In the case of PASH, there are no blood cells in the slit-like spaces, and the lesions do not exhibit any atypia or mitotic activity\textsuperscript{6}.

Since the spindle cells that cover the vascular-like-slit were immunopositive for CD34\textsuperscript{3, 5} and vimentin\textsuperscript{2, 3, 6} but immunonegative for Factor \( \text{VIII} \)\textsuperscript{2, 3}, they were also useful markers for making the histological diagnosis. Furthermore, PASH exhibits variable immunoreactivity for SMA\textsuperscript{5}. In this study, the spindle cells covering the vascular-like slits were positive for CD34 and, in part, SMA. The immunostaining pattern suggested that the spindle cells consisted of a spectrum of cells, ranging from relatively juvenile mesenchymal cells to myofibroblasts. The term pseudo-angiomatous stromal hyperplasia expresses only the stromal form of this lesion. It is often accompanied by hyperplasia of the ducts and lobular epithelium, as well as apocrine metaplasia and cyst formation\textsuperscript{2, 5, 7}. Some cases might not be diagnosed as PASH because the ductal proliferative changes are apparently more remarkable than those of the stroma. It is necessary to differentiate PASH from other types of benign breast tumors such as hamartomas, fibroadenomas and phyllodes tumors\textsuperscript{8-11}.

PASH occurs in premenopausal, perimenopausal or postmenopausal women who have taken hormone replacement therapy\textsuperscript{5, 8}, and in 23.8% of men who have gynecomastia\textsuperscript{9}. Furthermore, progesterone receptor immunoreactivity is often positive\textsuperscript{5, 6, 8}. Hence many authors have described PASH
as being hormone-dependent; in other words, PASH is hyperplasia of the stromal cells induced by an excessive response to progesterone. In this case the patient was perimenopausal when she came to our hospital, however, on immunostaining neither estrogen nor progesterone receptor was apparent in stromal cells. Thus, there was only indirect evidence of a hormonal etiology in this case.

Since she had been treated with loxoprofen sodium, bucillamine and famotigine for articular rheumatism, the possibility that the lesion was drug-induced was raised. There has been one case report of remarkable breast enlargement while taking bucillamine. Famotigine sometimes causes gynecomastia in men, and, rarely, lactation and swelling of the breasts in women. In this case, because the breasts had started to enlarge before she was treated with the drugs in 2002, and the lesions were asymmetric, the drugs might not have been the main cause of the nodules but may have exerted some influence on the growth of the nodules. The patient stopped taking these drugs in December 2003.

It is very difficult to diagnose of PASH by imaging alone, with MMG, US and MRI. On MMG, PASH exhibits no calcification, but usually a totally or partially regular border, and sometimes an irregular one. PASH is often detected in progressive asymmetrical breast tissues by MMG. On US, it exhibits variable findings, from homogeneous, low to iso- and high-echoic solid lesions to masses including a cystic structure. Nevertheless, PASH typically presents with a regular border and a hypo-echoic lesion. There have been a few case reports of MRI for PASH. In one case report, PASH exhibited mainly intermediate signals with some low-intensity regions using gadolinium-enhanced T1-weighted imaging, and some lesions included high- and low-intensity areas covered with a low-intensity capsule. In another case report, the findings from the time-intensity curve demonstrated almost the same pattern as a fibroadenoma, although the MRI was more useful for examining the size, border and nature of the tumor than the other imaging methods.

Since the FNA findings for PASH are not specific, it is insufficient for diagnosis, as in this case. Even when CNB is performed, it is necessary to keep the possibility of PASH in mind.

Although there has been a case report of PASH that was treated by tamoxifen, some authors have recommended local widespread excision. Nevertheless, PASH sometimes recurs after excision. Powel et al. reported a case in which bilateral mastectomy was performed for multiple recurrences. However, there have been no cases in which PASH became malignant. Moreover, some authors have reported that when the findings of imaging, US or MRI, and CNB are consistent with PASH and were able to exclude malignancy, resection is not necessary with close imaging follow-up.

In this case, we found a total of 9 masses in both breasts, one of which was diagnosed as PASH. Since PASH often occurs in multiples, the other 8 lesions could have been also PASH or other types of tumor. In order to definitively diagnose all the tumors, we considered it necessary to respect them all, because CNB was not sufficient for definitive diagnosis. Since 7 nodules were distributed all over the right breast and occupied many parts of the breast, we would have needed to perform right mastectomy to remove all the masses. However, the findings from all the imaging procedures indicated benign lesions, and the patient preferred to continue with conservative management. Thus we did not choose to perform such an aggressive surgical procedure on her breasts and decided to closely follow the lesions periodically. Even though the remaining tumors shrunk naturally 18 months later, it may have been appropriate to perform CNB on all residual nodules to confirm the diagnosis.

Acknowledgements

We thank Dr. Paul Peter Rosen (New York-Presbyterian Hospital Weill Cornell Medical Center), Dr. Goi Sakamoto (The Cancer Institute of Japanese Foundation for Cancer Research), Dr. Shu Ichihara and Dr. Suzuko Moritani (National Hospital Organization Nagoya Medical Center), and Dr. Yasuaki Nakashima (Kyoto University Hospital) for their significant advice.

A summary of this report was presented at the 13th annual meeting of the Japanese Breast Cancer Society in Kurashiki in 2003.

References

3) Milanezi MF, Saggioro FP, Zanati SG, Bazan R,