

The contrasting presentation and management of pseudoangiomatous stromal hyperplasia of the breast

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ABSTRACT

Pseudoangiomatous stromal hyperplasia of the breast is a benign entity characterised by dense, collagenous proliferation of mammary stroma, forming interanastomosing capillary-like spaces lined by slender spindle cells. These spaces are not true vascular spaces, hence the term “pseudoangiomatous”. We report two 14-year-old girls, who presented to us with pseudoangiomatous stromal hyperplasia of the breast. We believe that our patients represent two of the youngest ethnic Chinese females to be reported with this rare condition. The development of such a rapidly enlarging lesion often leads to anxiety and concern about malignancy, and emphasises the importance in appropriate diagnosis and management. We discuss the aetiology, clinical presentation, radiological and pathological features, as well as management of this unusual condition.

Keywords: collagenous proliferation of mammary stroma, hyperplasia of stromal myofibroblasts, pseudoangiomatous stromal hyperplasia, PASH

Singapore Med J 2008;49(3):e82-e85

INTRODUCTION

Pseudoangiomatous stromal hyperplasia (PASH) of the breast was first described in 1986 by Vuitch et al.⁽¹⁾ Since then, approximately 100 cases of this benign entity have been described in the literature, with only a handful of reports in teenagers, with the youngest patient reported being 12 years of age. Both our patients were 14 years old, representing two of the younger patients reported. To the best of our knowledge, our patients are the youngest ethnic Chinese girls to be reported with PASH of the breast.

PASH of the breast results from hyperplasia of stromal myofibroblasts in response to hormonal stimuli. It is benign, often presenting with clinical, radiographical and cytological findings mimicking those of fibroadenoma.⁽²⁻⁹⁾ Although PASH tends to grow over time, most cases can be cured by excision, and the prognosis is good.⁽¹⁰⁾

The development of such a rapidly enlarging lesion often leads to anxiety and concern about malignancy. Hence, the importance of appropriate diagnosis and management of this condition is emphasised. We report two cases of 14-year-old adolescent girls with PASH, each



Fig. 1 Photograph shows diffuse enlargement of the right breast as a result of PASH.

possessing very different presentations, and highlight the stark contrast in possible clinical presentations and subsequent management of the condition.

CASE REPORTS

Case 1

A 14-year-old nulliparous Chinese girl presented with a non-tender rapidly-enlarging right breast lump over four months. She did not have any significant past medical history, family history, history of oral contraceptive usage or trauma. Clinical examination revealed a 2-cm lump in the outer lower quadrant of the right breast without lymphadenopathy. Ultrasonography (US) assessment of the right breast showed a benign lesion. She underwent an excision biopsy, and histological features were consistent with PASH. 12 months postoperatively, she was well with no recurrence.

Case 2

Another 14-year-old nulliparous Chinese girl, without previous medical history or family history, presented with asymmetrical right breast enlargement over three months. She did not have nipple discharge, history of trauma, surgery or injections into the breast. She was not taking medications nor supplements. Backache featured as a consequence of the asymmetrical weight of her breast on her spine. Furthermore, she experienced social embarrassment especially when she was at school. On examination, there was diffuse enlargement of the right

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breast compared with the left (Fig. 1). The breast tissue felt tense. Her axillary lymph nodes were not palpable.

Mammography was hampered by dense glandular parenchyma. US showed non-specific benign changes with a few cystic spaces noted within. Magnetic resonance (MR) imaging showed marked enlargement of the right breast with skin thickening, oedematous changes and prominent ducts. Numerous enhancing areas, which had benign enhancement kinetics, were noted. Core biopsy revealed features suggestive of PASH.

After three months, there was significant enlargement of the right breast. The patient and her parents decided for right breast reduction mammoplasty. The surgery was performed with a modified Wise incision and medially-based dermal-glandular pedicle. 800 g of breast tissue was excised. The subsequent postoperative recovery was uneventful. The final histology of the specimen confirmed PASH. There was no evidence of malignancy. Nine months after the operation, the patient remained well with no signs of recurrence.

DISCUSSION

Most breast lesions presented during adolescence are benign, with fibroadenomas forming the bulk of the diagnoses. Occasionally, they may present with rapidly-growing breast masses with the possible causes being giant fibroadenomas, malignant phylloides tumour and soft tissue sarcomas. Another rare differential diagnosis would be PASH. PASH may grow very rapidly, as seen in our second case. This may be attributed to the hormonal milieu of adolescence. Such a rapidly growing mass often raises the suspicion for malignancy. Although rare in adolescence, the increasing public awareness of breast cancer often leads to patient and parental concerns.

Vuitch et al first described PASH in 1986 as a benign entity characterised by dense, collagenous proliferation of mammary stroma, forming inter-anastomosing capillary-like spaces. The term "pseudoangiomatous" describes the histological pattern which resembles, but does not actually constitute, an angiomatous proliferation. Early case reports described PASH in premenopausal women and elderly women taking oestrogen replacement therapy.⁽¹⁻³⁾ PASH has since been described in a wide range of patients including men,⁽⁷⁾ immunosuppressed patients,^(11,12) and teenagers.^(7,10,13,14) Both of our patients were 14 years of age when they presented, representing two of the youngest patients ever reported. In our review of recent literature, the youngest patient reported with PASH was aged 12 years at diagnosis.⁽¹⁴⁾

PASH presents either as an incidental microscopic finding or a clinically palpable lesion. The actual prevalence is difficult to estimate. In a report of 1,661 breast biopsies, seven patients (0.4%) had PASH.⁽⁴⁾ In another report of 200 consecutive breast biopsies, microscopic PASH was seen in 23% of benign or

malignant breast specimens, and was multifocal in at least 60% of cases.⁽²⁾ In clinically palpable lesions, PASH may occur in the nodular or diffuse form. Patients typically present with one or more discrete, painless, mobile, firm or rubbery masses, that can be bilateral and as large as 7 cm in diameter.⁽²⁾ Clinically, PASH may be indistinguishable from a fibroadenoma, as was the case in our first patient. Although most masses grow slowly, lesions that grow rapidly have been reported,⁽⁶⁾ particularly in immunosuppressed patients.^(11,12) Our second patient demonstrated how PASH could grow rapidly into a large mass, although she was immunocompetent.

The exact pathogenesis of PASH remains controversial. Initial theories suggested that the stromal changes in PASH are due to hormonal stimulation of the breasts.^(3,10) These changes may represent an aberrant reactivity of myofibroblasts to endogenous or exogenous hormones. Similar changes are seen on the normal mammary stroma during the luteal phase of the menstrual cycle, suggesting that PASH may develop as a response to progesterone in oestrogen-primed tissue.⁽¹⁾ PASH is also often found in premenopausal women, in older women on oestrogen replacement therapy and during pregnancy.⁽³⁾ The response of PASH to tamoxifen further reinforces the role of hormones in its development.⁽¹⁵⁾ Stromal cells in PASH have been found, on immunocytochemical staining, to be strongly positive for progesterone receptors. Opposing evidence to this theory include the small percentage of cases with oestrogen receptors (10%) or progesterone receptors (30%),^(3,7,10) occurrence in older women not on oestrogen replacement therapy, and the existence of rapidly-growing lesions that were completely negative for oestrogen and progesterone receptors.^(11,12)

The radiographical findings in PASH are non-specific,⁽⁸⁾ and may resemble those of fibroadenomas, i.e. a well-circumscribed dense homogenous mass lacking calcifications.^(4,5,8) The adolescent breast tissue is more fibrotic, obscuring identification of lesions, or leading some to interpret normal development as possible suspicious lesions. On US, PASH usually appears as a slightly heterogeneous but predominantly hypoechoic solid mass, with cystic spaces.^(4,5,8,16) As the use of MR imaging in assessing PASH has not been extensively studied, it was the topic of another paper, where the MR imaging findings of our second patient was correlated to histology.⁽¹⁶⁾ Current imaging modalities are not specific enough to make a firm diagnosis of PASH without tissue diagnosis.^(4,5,8)

Fine-needle aspiration cytology (FNAC) of PASH often results in acellular specimens. When tissue is present, the cytological findings are similar to those of fibroadenomas, although the smears are less cellular.⁽⁶⁾ The lower cellularity in PASH aspirates may be related to the associated stromal hyalinisation. However, sampling techniques also play a significant role in determining

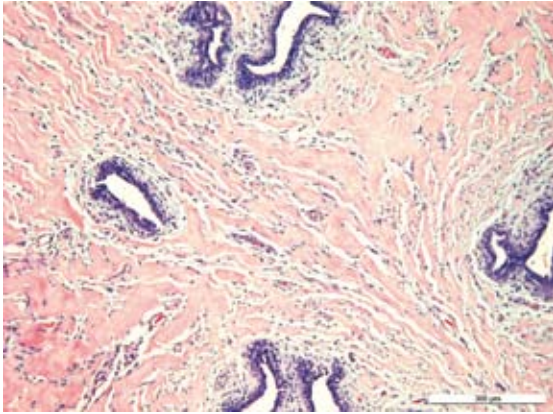


Fig. 2 Stromata among breast ducts are involved by PASH. Photomicrograph shows a complex pattern of anastomosing slit-like empty spaces in the dense collagenous stromata. The slit-like spaces are lined by myofibroblasts rather than endothelial cells.

overall cellularity of a fine-needle aspirate. The ductal epithelial component often assumes a nondescript club shape and sometimes, staghorn configuration. Epithelial cell clusters show variable sizes with medium to small groups, and stromal elements are minimal or absent. The background cells are composed of round to oval naked nuclei and spindle shapes. Occasionally, epithelial clusters show cellular dissociation and slight atypia. Although FNAC does not definitively diagnose PASH due to absence of specific cytological features, most cases would be correctly identified as benign, thus allowing appropriate management.⁽⁶⁾ Core biopsies, however, may be used reliably in establishing diagnosis.⁽⁵⁾

On gross pathological examination, PASH is usually a well-demarcated mass with a smooth external surface. The mass has been reported to range from one to 18 cm.^(2,12) The cut surface consists of homogeneous white, firm or rubbery fibrous tissue,^(1,2,10) that may contain small unilocular cysts.^(2,6) Areas of necrosis or haemorrhage are not usually present, except in tumours subjected to needle or aspiration biopsy.

Microscopically, PASH is characterised by a complex pattern of anastomosing slit-like empty spaces in dense collagenous stromata (Fig. 2). These spaces are not true vessels, but rather appear to arise by a process that involves disruption and separation of stromal collagen. The slit-like spaces are lined by myofibroblasts rather than endothelial cells. On immunohistochemistry, they are usually reactive for CD34, but to a lesser degree than endothelial cells.⁽¹⁶⁾

The histological features of PASH may sometimes lead to the misdiagnosis of low-grade angiosarcoma, as both have slit-like connecting spaces that are incompletely lined by spindle cells.⁽¹⁾ However, PASH typically has empty spaces with no endothelial lining, whereas in angiosarcoma, the spaces are filled by erythrocytes and lined with malignant endothelium.⁽¹³⁾ In young women, it is necessary to exclude giant fibroadenoma, which shows a characteristic histomorphological picture. PASH has

also occurred as an incidental finding in cases of invasive adenocarcinomas. However, a finding of PASH in a breast biopsy does not require an extensive search for associated malignancy. PASH is not considered premalignant; invasive or *in situ* carcinoma has not been reported within a PASH nodule.

The management strategies of PASH may be surgical or non-surgical. Surgery is generally recommended for definitive treatment. PASH tends to have a well-defined capsule, and complete excision with clear margins would be optimal in minimising recurrence. This was achieved in our first patient, who had excision biopsy of her lump with negative margins. However, in cases of diffuse PASH, as in our second patient, breast-conserving excision is difficult and mastectomy may be required to achieve adequate margins. Our patient was offered mastectomy and breast reconstruction. However, she opted for mammoplasty to reduce the size of her right breast, despite understanding the high risk of recurrence and possible need for subsequent operations. Clinical follow-up after excision is similar to that of fibroadenoma, including periodic clinical examination and imaging. In the event of relapse, a second resection with clear margins is usually sufficient.

Non-surgical options have also been described. Expectant management of the lesion may be acceptable especially when it is small, and triple assessment has been performed to exclude malignancy. An impressive response of PASH to tamoxifen has been reported,⁽¹⁵⁾ where the patient demonstrated marked response each time tamoxifen was commenced, but PASH recurred each time she stopped the therapy. Although tamoxifen appears to be effective, its effects may only be sustained with prolonged therapy. Long-term tamoxifen may not be ideal, especially after considering its potential side-effects.

PASH often grows over time and can recur locally. The recurrence rates range from 15% to 22%.^(1,10) The reason for recurrence could be attributed to growth of a residual mass after incomplete excision, the presence of multiple lesions that were not all excised, or *de novo* growth of PASH. In our two young patients, recurrence was a constant worry, especially in the second case, where residual disease was a major concern. Although we have illustrated how reduction mammoplasty may have a role in the treatment of massive diffuse PASH, it remains to be seen if or how soon the disease would recur in her. On the other hand, it has also been reported that PASH may regress spontaneously.⁽¹⁰⁾

In conclusion, PASH is a rare benign entity that occasionally presents in young women as a rapidly enlarging breast mass. The attending clinician would have to consider commoner differential diagnoses, such as giant fibroadenomas, malignant phylloides tumour and sarcomas. PASH would be a rare differential diagnosis in this clinical setting. Clinical and radiological differentiation of these conditions are very difficult, and

histological assessment would be necessary to definitively diagnose each of these conditions. PASH is a benign condition with good prognosis,^(2,10) and there has been no report of distant metastases or death. However, until more is learnt about this rare condition, long-term follow-up is recommended for all these patients.

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