CASE REPORT

Pseudoangiomatous stromal hyperplasia causing massive breast enlargement

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Accepted 26 September 2015

SUMMARY

Pseudoangiomatous stromal hyperplasia (PASH) of the breast is a benign mesenchymal proliferative process, initially described by Vuitch *et al.* We report an unusual case of a 46-year-old woman who presented with a 6-week history of bilateral massive, asymmetrical, painful enlargement of her breasts, without a history of trauma. On clinical examination, both breasts were markedly enlarged and oedematous, but there were no discrete palpable masses. Preoperative image-guided core biopsies and surgery showed PASH. PASH is increasingly recognised as an incidental finding on image-guided core biopsy performed for screen detected lesions. There are a few reported cases of PASH presenting as rapid breast enlargement. In our case, the patient presented with painful, asymmetrical, massive breast enlargement. Awareness needs to be raised of this entity as a differential diagnosis in massive, painful breast enlargement.

BACKGROUND

Although a number of cases are described there is limited literature from a radiological perspective on this unusual pathology. As radiologists play an important role in multidisciplinary teams, their awareness of this entity needs to be raised. We report a case of a 46-year-old woman who presented with subacute asymmetrical, gross enlargement of both breasts and a confirmed histological diagnosis of pseudoangiomatous stromal hyperplasia (PASH).

CASE PRESENTATION

A 46-year-old woman presented with a 6-week history of bilateral massive but asymmetrical enlargement of her breasts, with associated pain. She had a history of bilateral breast reduction surgery performed 18 years prior, although no associated pathology was available for review. There was no history of trauma. The patient had had a Mirena coil for contraception placed 6 months prior to her presentation. She was initially treated with antibiotics for presumed mastitis. Because of the lack of improvement, she was subsequently referred to our breast assessment centre. On clinical examination, both breasts were markedly oedematous, but no discrete, palpable masses were identified.

INVESTIGATIONS Imaging

The mammogram showed 25–50% density with a bilateral complex glandular pattern. No focal suspicious area was identified (figure 1A, B). The

mammographic density of the lateral aspect of the left CC view was a cyst on ultrasound (figure 1B arrow).

Ultrasound of both breasts showed multiple, heterogeneous, oval-shaped and round-shaped areas with both well and poorly defined margins, interspersed with cystic spaces, and marked oedema within the superficial tissues of both breasts (figure 1C). The masses, which had predominantly hypoechoic echoes but with some heterogeneous areas, were oriented parallel to the chest wall. Posterior enhancement was evident in some of the masses. No calcifications were evident.

MRI showed large breasts. T2 fat-saturated sequence showed a diffuse, complex, whorled pattern with linear bright signal within the fibrous stroma of multiple oval-shaped lesions. A diffuse enhancement pattern was seen in these areas throughout both breasts (figure 1D) in addition to clumped enhancement in multiple focal regions.

Ultrasound-guided 14 G core biopsies ×5 were taken of multiple different widespread hypoechoic areas, all revealing a diagnosis of PASH.

Following this, an excisional biopsy was performed after imaging-guided hook-wire localisation of the dominant lesion from each breast. A needle was placed in the fresh excised specimen under ultrasound to confirm the lesion location.

Histopathology

Macroscopic examination of each excisional biopsy revealed a well-circumscribed, rubbery, pink-white, solid mass, measuring 24×16×14 mm on the right side and 25×16×14 mm on the left side. Examination of the cut surface of each specimen revealed abundant fibrous tissue throughout, admixed with normal fatty tissue. Similar appearing areas were noted throughout the breast tissue from the reduction mammoplasties.

Histological examination of the core biopsies and the reduction mammoplasty specimens revealed similar features (figure 2). There were normal breast ducts and lobules lying in abundant dense fibrous stroma. Complex, anastomosing, slit-like spaces were evident throughout the stroma. These spaces were empty and lined by a discontinuous single layer of flat, benign spindle cells. There was no nuclear atypia or mitotic activity.

Superimposed fibroadenomatoid hyperplasia was seen in the hypoechoic areas, characterised by an expansion of glandular as well as stromal elements. The stroma in these specimens also showed extensive involvement with PASH. No in situ or invasive malignancy was identified.

To cite: Bourke AG, Tiang S, Harvey N, *et al.* *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204343

Figure 1 (A and B) The mammogram showing 25–50% density with a bilateral complex glandular pattern. No focal suspicious area was identified. The mammographic density of the lateral aspect of the left cranio-caudal view on ultrasound was a cyst. (C) Ultrasound of both breasts showing generalised heterogeneous breast pattern with multiple oval or round masses that were well-circumscribed, and oriented parallel with the chest wall. The echo pattern was predominantly hypoechoic, but there were heterogeneous areas. Some posterior enhancement was noted in some lesions. No calcifications were seen. Normal vascularity was noted. There are interspersed cystic spaces. Marked oedema within the superficial tissues of both breasts was noted. (D) MRI showed large breasts. A diffuse enhancement pattern was seen in these areas throughout both breasts ((D) delayed contrast enhanced (DCE) phase at 3.5 min) in addition to clumped enhancement in multiple focal regions.

Immunohistochemical staining confirmed that the spindle cells lining the slit-like spaces were positive for CD34, and negative for CD31, von Willebrand factor and D2–40. The stromal spindle cells were focally weakly positive for both smooth muscle actin and progesterone receptor but were negative for oestrogen receptor.

Figure 2 High power view (H&E stain) demonstrating numerous anastomosing slit-like spaces admixed with breast epithelial elements. The spaces are lined by a single layer of cytologically bland spindle cells.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for subacute, enlarging breasts are wide, and include many benign and malignant conditions, both inflammatory and non-inflammatory. Imaging has shown a complex glandular pattern bilaterally with areas of well-defined sonographic hypoechogenicities. The complex glandular enhancement may be seen in angiosarcomas of the breast, however, bilateral symmetrical lesions would be highly unlikely and the presence of the well-circumscribed hypoechoic areas are reassuring as they are often a sign of a non-aggressive process. Therefore, the imaging features described here narrow the differential diagnosis substantially. The potential diagnoses to consider for the hypoechoic areas would be those of benign breast masses such as multiple hamartomata or fibroadenomata. A hamartoma presents mammographically as a well encapsulated mass with heterogeneous density due to the presence of both soft tissue and fat resulting in a ‘breast-within-breast appearance’. There was no encapsulation in this case. Multiple fibroadenomata often presents as well-circumscribed hypoechoic masses on ultrasound. The complex glandular enhancement shown in this case is not a feature.

TREATMENT

Bilateral mammoplasty was performed in 2012. Image-guided localisation of the two hypoechoic areas was undertaken to ensure excision of these areas.

OUTCOME AND FOLLOW-UP

Because of continued enlargement of the breasts, the patient underwent bilateral mastectomy with immediate reconstruction in June 2015. The histopathology showed multiple irregular grey stromal nodules with a white cut surface and a rubbery consistency throughout both breasts. The right breast weighed 2200 g and measured 320×190×100 mm. No tumour was identified. The left breast weighed 2450 g and measured 330×230×95 mm. Microscopically, all specimens showed similar features. Sections showed female breast including ducts and lobular units encased in marked dense collagenous stroma, which were separated by bland stellated to spindled cells arranged in anastomosing cords forming pseudovascular spaces. Other benign breast changes included fibrocystic change and fibroadenomatous hyperplasia. There was no in situ carcinoma or invasive malignancy.

Conclusion: Left and right breast—Benign breast change with marked collagenous fibrosis, including a significant component of PASH.

DISCUSSION

As described by Vuitch *et al*,¹ PASH is a stromal proliferation of the breast, occurring most commonly in premenopausal women.² It has also been documented in males in association with gynaecomastia.³ It has a wide clinicopathological spectrum, ranging from incidental microscopic foci to clinically and mammographically evident breast masses or diffuse enlargement.^{2 4 5} Non-tumour forming microscopic PASH is relatively common and may be an incidental finding in up to 23% of breast biopsies.⁶ Tumour forming PASH is uncommon, with <150 cases reported since its first description in 1986.^{5 7} Asymmetric, diffuse bilateral breast enlargement by PASH, as described in this case, is very rare, with only one similar case previously reported, to our knowledge.⁸

Pathological features

The diagnosis relies on histological examination of biopsy or excisional samples. It may be seen as an isolated lesion, or in association with any other breast lesion, benign or malignant.⁵ The classical pattern, as described by Vuitch *et al*,¹ comprises anastomosing cleft-like spaces within a sclerotic stroma, seen both between and within the breast lobules. These spaces are lined by spindle-shaped myofibroblasts, simulating endothelial cells and contributing to the appearance of a vascular lesion. Nuclear atypia or significant mitotic activity is not seen. The admixed epithelium may be normal, although mild hyperplasia or papillomatosis has been described.¹ Other studies have reported gynaecomastia-like changes.² Subsequent studies have described a spectrum of histological appearances, ranging from the classical description as outlined above, through to more cellular, proliferative lesions.⁴ These lesions are comprised of fascicles of plump spindle cells that may obscure the underlying pseudoangiomatic spaces.

Immunohistochemically, the spindle cells show a staining profile consistent with myofibroblastic differentiation, with positive staining for vimentin, CD34 and smooth muscle actin. Markers of endothelial differentiation, such as CD31 and von Willebrand factor, are negative.^{4 5}

Although uncertain, it is suspected that PASH represents a localised stromal overgrowth in response to hormonal stimuli, particularly progesterone. The stromal cells in PASH lesions are positive for progesterone receptor,⁴⁻⁹ and some studies have reported an association with hormonal therapy.²

Histologically, PASH can be confused with low-grade angiosarcoma. It is important to differentiate the two entities, as angiosarcoma is a malignant process requiring aggressive treatment with wide local excision and chemotherapy. This distinction can usually be made readily on histopathological examination. Angiosarcoma is characterised by an infiltrative growth pattern with cytological features of malignancy such as a nuclear hyperchromasia, pleomorphism and increased mitotic activity. In contrast, PASH usually has a circumscribed outline, while its constituent cells are cytologically bland.¹

Immunohistochemically, angiosarcoma will be positive for endothelial markers such as CD31 and von Willebrand factor.³ Other differential diagnostic considerations, particularly in the context of a tumour forming lesion, include myofibroblastoma, fibroadenoma and mammary hamartoma. PASH lesions with a fascicular growth pattern are more likely to cause diagnostic confusion.⁵

Imaging

There has been little radiology literature describing PASH findings since it was first detailed in 1989.^{1 10 11} PASH is a common pathology that does not often present with an imaging finding. PASH is identified in up to 23% of biopsy specimens with gynaecomastia,³ it is important to be familiar with imaging features so that unnecessary surgery can be avoided. Most cases have no mammographic abnormalities, but when there is a mammographic finding, the most common appearance is that of a solitary, non-calcified mass, which may be palpable or localised increased stroma.^{4 12 13} Stellate opacities, architectural distortions and calcifications are uncommon. According to Hargaden *et al*,¹⁴ 69% of their 149 biopsy-proven PASH patients had no mammographic abnormality, as was the case in our patient.

The ultrasound characteristics of PASH can vary. In a literature review by Celliers *et al*,¹² the most common sonographic finding was that of a well-defined, hypoechoic mass. Rarer findings include a heterogeneous mass with cystic components. The imaging features are not specific, although they often suggest a benign process. MRI appearances have been described as clumped, non-mass-like areas of persistent or plateau enhancement.

Outcomes for PASH

PASH is not thought to be associated with malignancy, nor is it considered premalignant.¹⁵ To date, there has been only one reported case that suggested possible malignant transformation of a PASH lesion,¹⁶ and rare cases have been reported in PASH-associated ductal carcinoma in situ (DCIS).⁸ PASH can co-exist with a malignant process, and any suspicious imaging features would warrant tissue sampling. In a review of 200 breast specimens, invasive adenocarcinoma was found in 10% of PASH cases.^{12 14}

Mass lesions in PASH often grow over time and may recur after excision biopsy, with a recurrence rate between 15% and 22%.⁸ The findings of a PASH-associated neoplastic lesion may be coincidental, as a study has shown that the risk of developing malignancy is smaller in those with PASH than in those without.¹⁵

For the group of patients with PASH-concordant radiological and histological findings, close observation with serial imaging is considered safe management. Excision may be considered on the basis of patient's preference, in rapidly enlarging lesions, as in our case, or if there is a strong family history of breast cancer.

In summary, PASH should be considered in the differential diagnosis for rapid massive breast enlargement. The imaging characteristics for PASH are usually not specific, although there are usually features to suggest a benign lesion on ultrasound.

Diagnosis is made only if imaging and histological features are concordant. A review of the current literature suggests that surgical excision may not be indicated when a diagnosis of PASH alone is made.^{6 15} Non-surgical management with close imaging surveillance is appropriate in most patients.

Learning points

- It is important to recognise pseudoangiomatous stromal hyperplasia (PASH) as a cause for rapid and asymmetrical enlargement of both breasts.
- Radiology awareness of this differential diagnosis may expedite patient care.
- PASH has been described on MR as clumped non-mass-like enhancement. In this case, there was also a benign enhancement in the stroma diffusely throughout both breasts.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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