Pseudoangiomatous Stromal Hyperplasia (PASH) of the breast is a rare condition that consists of the proliferation of the breast myofibroblastic stromal cells, lining anastomosing vascular slit-like spaces. This condition is not considered a pre-malignant lesion and affects mainly premenopausal women. Its etiology is still uncertain, but its behavior points to a hormonal cause. It has a varied clinical presentation and can be diagnosed as an incidental finding of biopsies or with the manifestation of clinical signs and symptoms. As for the diagnosis, it can be performed with the correlation between clinical data, imaging and histopathological analysis. Due to its rare nature, there are still no prospective studies regarding treatment, but, in most cases, clinical and radiological follow-up is a safe strategy. The aim of this paper is to synthesize the data available in the literature about this condition, which, although benign in nature, can bring important aesthetic, musculoskeletal and psychological repercussions.

**KEYWORDS:** breast diseases; angiomatosis; hyperplasia; diagnosis; signs and symptoms; therapeutics.

**INTRODUCTION**

Pseudoangiomatous hyperplasia of the breast stroma or pseudoangiomatous stromal hyperplasia (PASH) is a rare condition that consists of the benign proliferation of myofibroblasts in the breast stroma, forming anastomosing canaliculi similar to vascular clefts. It was first described in 1986, by Vuitch et al.1, who classified the lesion as “mammary stromal proliferations that simulated vascular lesions.” PASH is not related to malignant lesions or considered a premalignant lesion2 and affects mainly pre-menopausal women3,4. Its etiology is still uncertain, but the main hypothesis is an aberrant hormonal stimulation and responsiveness as a cause3,5. PASH can be associated with other benign and malignant lesions of the breast. Its clinical presentation has a varied spectrum, being diagnosed incidentally after the histological analysis of biopsy samples performed to evaluate other lesions, as nodules or palpable masses and/or breast enlargement5,6. Sometimes we run into situations of difficult diagnosis and breast changes with intriguing behavior, leading us and our patients to great distress, subjecting them to aggressive and sometimes unnecessary interventions. The purpose of this review is to contribute to a better knowledge and understanding of PASH, improving the reasoning and the approach of our patients.

**ETIOPATHOGENESIS**

Although the etiology still remains uncertain, a widely accepted theory is that there may be a hormonal cause that generates PASH, based on several observations5,8. It is difficult to establish risk factors and/or the initiation of this lesion, as there is a strongly accepted hypothesis that neoplastic lesions that have a hormonal cause do not depend on a toxic or infectious specific agent to trigger its changes. In this case, for various reasons, there is an exacerbated reactivity to endogenous or exogenous hormonal stimuli, which provides mutations in the genetic material of cells sensitive to these hormones6.

The histopathological and immunohistochemical analysis usually shows the expression of hormone receptors, especially progesterone, in myofibroblasts from PASH-positive samples. This is the first observation that leads to a hormonal cause5. Another fact that points to this etiology is the distribution of the prevalence of this breast lesion according to age: the lesion is often present in women in the pre and perimenopause period3,4,10, and the clinical presentation in those who have already gone through menopause is usually minor injuries, or lesions associated with hormone replacement5. A case of lesion reduction with the use of tamoxifen also sheds light on the possibility of hormonal influence11. When PASH manifests itself in males, it is...
usually associated with gynecomastia. Another characteristic that corroborates this hypothesis is the variation in the size of the lesion observed according to the menstrual cycle. These facts all contribute to the thought that hormones, whether endogenous or not, act by stimulating the stromal cells of the breast, culminating in hypervascularization of extracellular matrix rich in collagen, characteristic findings of PASH.

In addition to the influence of progesterone on the genesis and evolution of PASH, another hormone was raised as a possible contributing factor in the process: prolactin. This peptide is a fundamental hormone to promote the proliferation and differentiation of the breast parenchyma and milk production. Some situations, such as hyperthyroidism, can cause an increase in circulating levels of this hormone, that is, a hyperprolactinemia. This condition leads to increased secretion by epithelial cells and expression of nuclear factor kappa B (NF-κB), which results in an inflammatory response in the cells of the breast epithelium. Therefore, there may be an association of prolactin levels with the development of PASH.

**CLINICAL MANIFESTATIONS**

PASH predominantly affects women in the pre or perimenopause, and those in the post-menopause, especially the ones under hormone replacement therapy. It can also more rarely affect people of the male sex and individuals in childhood. When comparing the clinical presentation among women in the post-menopausal phase with those who have not yet undergone this physiological event, the lesions are usually larger in women in pre and perimenopause.

PASH is a condition that has a wide spectrum of clinical presentations. It can manifest symptomatically, with an incidental diagnosis when analyzing samples of biopsies that were performed to evaluate other lesions, whether benign or not. The prevalence of incidental diagnosis of PASH in these situations has been reported in studies, ranging from 6.4% to 23%.

The proportion of cases presenting as symptomatic and asymptomatic is variable between published studies. There are studies that report that the predominant form is symptomatic, while others report a predominance of diagnosis by means of an incidental finding on biopsy.

The proportion of male individuals who present gynecomastia and have findings suggesting PASH at biopsy ranges from 24% to 47%, as it highlights the need to consider PASH a differential diagnosis or an associated change in male individuals who complain of gynecomastia.

Among symptomatic individuals, PASH can manifest itself as a palpable nodule or localized mass, which can be clinically similar to fibroadenoma, or a rapid, diffuse and accentuated growth of unilateral or bilateral breasts (which can be symmetrical or asymmetrical). A case of presentation as an axillary nodule has also been reported. Depending on the proportion of breast growth, this manifestation can have aesthetic and musculoskeletal repercussions that are the motivation for seeking medical care.

**DIAGNOSIS**

The diagnosis of PASH is based on a set of clinical, radiological and histopathological data. The clinic, as mentioned in the previous topic, has a variety of presentations.

Macroscopically, when PASH forms a palpable mass, it appears as a firm, well-defined, circumscribed and unencapsulated mass of 1 to 12 cm in size. The cut surface shows a light brown and homogeneous color; in some cases, the lesion may be multinodular. For the histopathological analysis, a sample of...
the lesion can be obtained by incisional, core or excisional biopsy. The typical finding is well described and generally sufficient for diagnosis. There is proliferation of collagenized, hyalinized and acellular connective tissue, filled with spaces in the form of anastomotic slit-like spaces, devoid of red blood cells and lined by flattened and fusiform stromal cells — myofibroblasts, like endothelial cells, simulating vascular channels. The presence of intermixed terminal duct lobular units is observed (Figure 3)\textsuperscript{1,5}. Features that are commonly associated with malignancy, such as pleomorphism or nuclear atypias and mitosis figures, are generally not found in PASH\textsuperscript{4,5}.

PASH can be classified in two ways, according to the histological aspect of the lesion: the simple form and the fascicular or proliferative form. The simple type exhibits mainly anastomosing spaces, while the proliferative or fascicular type is characterized by areas of spindle cell proliferation, simulating myofibroblastoma\textsuperscript{5}.

Due to the similar microscopic or macroscopic characteristics of the lesion, PASH must be distinguished from low-grade angiosarcoma, other vascular tumors and phyllodes tumor\textsuperscript{8,20}. What helps with this differentiation, in addition to the morphological benign characteristics, is the immunohistochemical staining for some myofibroblast markers. In PASH, stromal cells show positive staining for hormone receptors (progesterone more often, and estrogen to a lesser extent), actin, desmin, and for CD34. As for other markers, they are usually negative, such as cytokeratins, vimentin, calponin, S100, and endothelial markers, factor VIII and CD31. Immunohistochemical staining has also been reported in one study to be negative for the lymphatic endothelium marker, D2-40 or podoplanin\textsuperscript{4,5,13}.

Biopsy is indicated only when another lesion, other than PASH, is suspected in imaging analysis. Therefore, when there is agreement between clinical and imaging findings, in which both suggest a benign lesion, there is no need to perform this procedure. In turn, when indicated, the biopsy is sufficient to diagnose PASH. Alterations can be unifocal, multifocal or diffuse and can be found associated with other benign lesions, such as fibroadenoma and gynecomastia, pre-malignant or even malignant conditions, such as phyllodes tumor. If a hidden malignancy is suspected, surgical excision is recommended. Fine needle aspiration puncture has no specific findings and should not be performed for diagnosis\textsuperscript{8}.

**IMAGING**

In general, on imaging studies, the lesions present characteristics of benignity. Mammography, ultrasonography (especially in cases of inconclusive mammography and in people of an earlier age) and magnetic resonance imaging (which is not routinely used, but can help with lesion assessment and surgical planning) can be used as diagnostic tools\textsuperscript{16}.

At mammography, the most common findings are a non-calcified solitary nodule and localized stromal enlargement\textsuperscript{22}. An irregular density can also be seen\textsuperscript{22}. Therefore, PASH with a presentation of a single nodular lesion has the typical characteristics of a benign finding at mammography. Usually, in these cases, it can be classified as BI-RADS 2 or 3; in cases where it is a diffuse lesion, we can find a BI-RADS classification \textsuperscript{4,13,23}.

Ultrasound findings are a well-defined hypoechoic mass of varying shapes and may present posterior echogenic enhancement. However, this propaedeutic method can present itself without changes in normality\textsuperscript{8,22}.

The findings that are found in nuclear magnetic resonance are varied and usually non-specific. It can present an isointense image in relation to the normal T1 mammary parenchyma, in addition to hyperintense reticular and cystic areas. Regarding the pattern after contrast injection, an initial rapid enhancement has already been observed, followed by a slow and gradual delayed enhancement\textsuperscript{24}.

These imaging findings have nonspecific patterns and have an important role in assessing the extent of the lesion, evaluating suspicious characteristics of malignancy in order to indicate an extension of the investigation and, in the case of ultrasound, to be able to guide the biopsy. In addition, they are useful in medical follow-up, indicating signs of evolution of the lesion.

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**Figure 3.** Pseudoangiomatous stromal hyperplasia of the breast: Dense and collagenized breast stroma with anastomosing channels lined by myoepithelial cells, simulating vascular channels. Presence of intertwined duct-lobular epithelial units. Hematoxylin and Eosin, at a magnification of 10 and 40 times.
THERAPEUTIC APPROACH

The American Society of Breast Surgeons does not recommend routine surgical excision of PASH when suspected on imaging or diagnosed in an incisional biopsy sample. Clinical and radiological follow-up is a safe strategy. Surgical treatment can be performed in those cases in which there is genetic predisposition to cancer and important aesthetic deformities or repercussions. Surgical treatment can also be an option based on the patient’s preference.

A surgical approach can be indicated at any time during the clinical-radiological follow-up, if any of the following conditions are found: progression of the lesion (that is, increase in the size of the lesion), inconclusive findings regarding histology and/or suspicious aspects of malignancy in radiological propedeutics. PASH can be often considered a condition classified as BI-RADS 2 or 3, as mentioned above, and when it is incidentally diagnosed, it does not require any active management.

The initial approach is based on the clinical manifestations and the findings on imaging and pathological analysis. It should be clinical observation, vacuum-guided excision or surgical excision and, in some selected cases, unilateral or bilateral mastectomy. The choice of the surgical modality can be based on the size of the lesion, the patient’s desire and the surgeon’s experience.

Tamoxifen, despite having already been reported as a management strategy, is not recommended, due to its side effects and the contraindication for use in pre-menopausal women.

EVOLUTION

It is known that PASH is not considered a premalignant lesion. Although there are reported cases of associated malignant lesions, sometimes in the same focus, there is not enough data to affirm that PASH is a precursor lesion, to the detriment of the hypothesis that it had just overridden the malignancy. However, there is an isolated case report in which an unequivocal evolution towards malignant lesion was observed. Nevertheless, the database is not very extensive and there is no study capable of proving causality.

Most of the studies and published reviews have not demonstrated evolution to malignant lesions. They even demonstrate a lower proportion of malignant lesions in those patients who were diagnosed with PASH, without a proven relationship. One possible explanation, however, is that clinical-radiological follow-up of PASH allows for an early detection of possible malignancies that arise, but without having PASH as the cause.

The risk of progression (increase in the lesion that was primarily diagnosed as PASH, during clinical-radiological follow-up) may be influenced by the result of the biopsy of a fragment of the lesion (if there is any condition other than PASH), symptoms (palpable mass or accentuated increase in the breasts) and size (> 30 mm). The risk of recurrence or emergence of new outbreaks of PASH varies from 0.4% to 23%.

FINAL CONSIDERATIONS

PASH is a benign and rare condition of the breasts that was first described approximately 34 years ago, but which still does not have a consensus on its etiology, evolutionary behavior and ideal treatments, despite being increasingly standardized. Most published studies on this condition consist of case reports and case series, which limits decision making.

However, it is important that PASH be part of the collection of differential diagnoses for patients who seek care with any symptoms related to the breasts. In spite of its benign nature, it can cause uncomfortable symptoms, and the professional attending a case should individualize, based on clinical examination, complementary radiological study, histopathological analysis and the patient’s desire, the best treatment and follow-up strategy.

AUTHORS’ CONTRIBUTIONS

J.R.A.: Data curation, Formal analysis, Writing – original draft. C.B.N.: Writing – review & editing. C.E.M.L.: Conceptualization, Methodology, Supervision, Writing – review & editing.

REFERENCES


