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CASE REPORT

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Gynecomastia in type-1 neurofibromatosis with features of pseudoangiomatous stromal hyperplasia with giant cells. Report of two cases

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Abstract We describe the histological finding in two cases of gynecomastia in patients with von Recklinghausen's disease. The histological and immunohistochemical features of the two cases were reviewed and compared with those of five cases of gynecomastia in men without clinical evidence of neurofibromatosis. In both patients bearing von Recklinghausen's disease, the breast stroma showed features consistent with pseudoangiomatous stromal hyperplasia (PASH). It was characterised by anastomosing empty spaces lined by spindle and multinucleated giant cells which were positive with CD34 and anti-vimentin antisera and negative with anti-FVIII and CD31 antisera. In two of five of the control cases without neurofibromatosis, the mammary stroma showed focal areas with features of PASH, but no multinucleated giant cells were present in any case. PASH with giant cells should be recognised as a feature of gynecomastia in von Recklinghausen's disease. The presence of multinucleated giant cells is very unusual and, although more cases have to be studied, these cells seem to be a feature of PASH occurring in patients with von Recklinghausen's disease.

Keywords Breast · Pseudoangiomatous stromal hyperplasia · Giant cells · Neurofibromatosis

Introduction

Gynecomastia in children or adolescent males with von Recklinghausen's disease is not uncommon. However, only a few cases have been previously described with detailed histological findings [3, 4, 6, 8, 9, 12], and most of these are recorded as cases of pseudogynecomastia due to lipomatous or neurofibromatous proliferations of the mammary region [4, 6, 8] or as hamartomatous lesions of nerves and their supporting stroma [12]. Here, we describe two cases of gynecomastia in young males bearing type-1 neurofibromatosis. Both cases showed typical histological features of pseudoangiomatous stromal hyperplasia of the breast (PASH) [11, 13]. The clinicopathological features of the present cases are compared with those of gynecomastia occurring in five patients without evidence of neurofibromatosis.

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Case histories

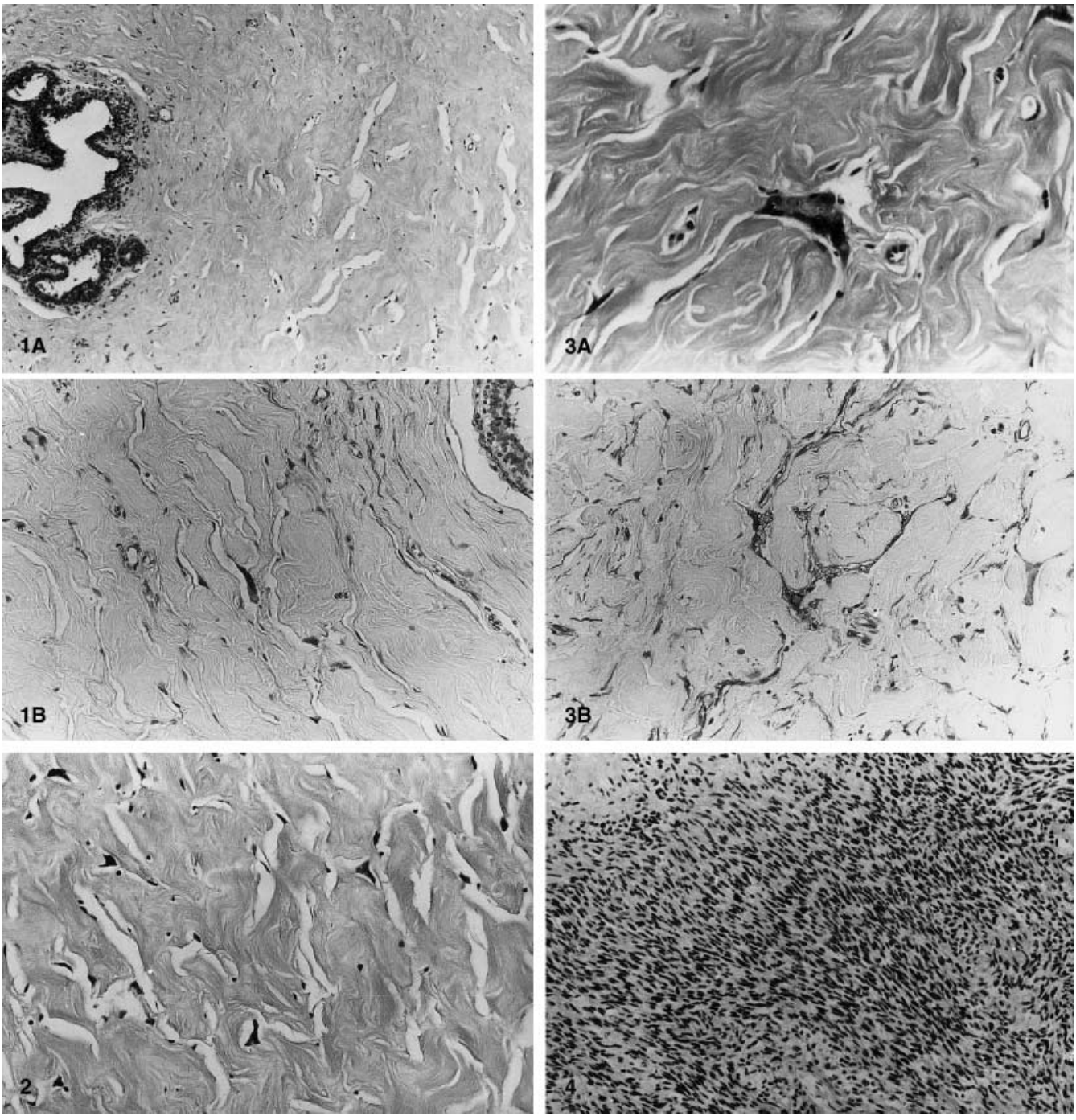
Case 1

In 1995, a 16-year-old boy with a long standing history of von Recklinghausen's disease, including cafè au lait spots and skeletal abnormalities, presented with severe respiratory distress. Upon computed tomography, a large intrathoracic mass of about 20 cm in its major axis was discovered. The patient shortly developed severe cardiac arrhythmia and died before any possible treatment. At post-mortem examination, the posterior and medial parts of the mediastinum were replaced by a large (24×15×15 cm) multinodular tumour, which entirely enveloped the aorta, superior vena cava and pulmonary veins. It was composed of grey–whitish tissue with large areas of necrosis and showed focally cystic changes.

A bilateral and symmetric enlargement of the breasts was also noted, each gland measuring about 8 cm across. On cut section, the breast tissue appeared homogeneous, whitish in colour and fibrous in consistency. Cafè au lait spots were the only lesions present in the skin. Numerous plexiform tumours were found in the retroperitoneal and abdominal soft tissues. The prostate was normal in size and soft in consistency.

Case 2

In 1997, a 6-year-old boy was admitted to the Service of Reconstructive Surgery because of a marked bilateral enlargement of the breasts. The family history of the patient was apparently negative for von Recklinghausen's disease. However, at physical examination, seven large cafè au lait spots (ranging from 2 cm to 6 cm in major axis) in the skin of the lower limbs and trunk were noted, including three macular lesions in the skin of the right inguinal region (inguinal freckle sign). These findings, according to the internationally accepted criteria, are diagnostic for type-1 neurofibromatosis, meeting at least two of the required features [5]. No other abnormalities



were noted. From each breast, a 9-cm across part of whitish, fibrous tissue was removed. No biopsy was obtained from the skin lesions.

Materials and methods

Tissues were fixed in 10% buffered formalin, processed routinely and stained with haematoxylin-eosin (HE) and Giemsa stain. For immunohistochemical studies, the avidin–biotin peroxidase complex method was used. Antisera employed are shown in Table 1, together with their respective sources and dilutions. Five randomly selected cases of gynecomastia in patients without clinical evidence of neurofibromatosis were reviewed in order to compare their histological features to those of the present cases.

Fig. 1 Case 1 (**A**) and case 2 (**B**). The mammary stroma consists of dense fibrous connective tissue characterised by numerous cleft-like empty spaces simulating vascular channels (haematoxylin and eosin; **A** ×75; **B** ×120)

Fig. 2 Case 1. The pseudovascular spaces appear variously anastomosed and are lined both by spindle elements and multinucleated giant cells (haematoxylin and eosin ×120)

Fig. 3 Case 2. **A** Giant cells show numerous nuclei peripherally located (haematoxylin and eosin; ×310). **B** The spindle elements and the multinucleated giant cells lining the pseudovascular spaces are distinctly CD34 positive (avidin biotin peroxidase ×120)

Fig. 4 Case 1. The mediastinal tumour is constituted by bundles of spindle cells showing wavy nuclei. Areas of necrosis are also evident (*top left*) (haematoxylin and eosin; ×120)

Table 1 Antisera for immunohistochemistry. *M* monoclonal; *P* polyclonal; *SMA* smooth muscle actin; *ER* estrogen receptor; *PR* progesterone receptor

Antisera	M/P	Source	Dilution
CD34	M	Ylem	1:50
Vimentin	M	Dako	1:180
Cd31	M	Dako	1:20
Factor VIII	P	Dako	1:1000
SMA	M	Sigma	1:1000
S100 Protein	P	Dako	1:1000
Laminin	P	Dako	1:150
PR	M	Ylem	1:50
ER	M	Dako	1:100

Histological findings

In both cases, specimens from breast tissue revealed that the enlargement of the glands was predominantly due to the stromal component. This consisted of a dense, collagenous fibrous tissue characterised by numerous cleft-like open spaces, variously anastomosed, simulating vascular channels (Fig. 1A, B). The clefts appeared empty, devoid of red cells and were lined both by spindle and multinucleated giant cells (Fig. 2). These latter were floret-like in appearance and showed long cytoplasmic processes which lined the pseudovascular channels (Fig. 3). In some areas, the giant cells that bordered pseudovascular spaces were somehow reminiscent of the features of giant cell fibroblastoma [5].

Nuclear atypia and mitoses were absent either in spindled and in multinucleated cells. Numerous mast cells were also seen scattered throughout the mammary stroma in both cases. The glandular component was constituted in both cases by ducts with weak to moderate epithelial hyperplasia showing micropapillary projections. In case 2, small aggregates of ductules reminiscent of lobular units were also focally evident.

Immunohistochemically, the cells lining the pseudovascular spaces were positive with anti-vimentin and anti-CD34 antisera (Fig. 4), while S100 protein, desmin, smooth muscle actin and laminin antisera were consistently negative, as well as oestrogen and progesterone receptor antibodies. Anti-factor VIII and CD31 antisera stained small capillary vessels only, throughout both lesions.

The mediastinal tumour of case 1 showed histological (bundles of spindled cells showing hyperchromatic, wavy nuclei with high mitotic activity) and immunohistochemical (focal S100 protein reactivity) features consistent with malignant peripheral nerve sheath tumour (MPNST; Fig. 5), whereas the visceral plexiform tumours were classical benign neurofibromas. The prostatic tissue in case 1 showed a moderate degree of glandular hyperplasia and a discrete increase of the stromal fibromuscular component.

In three of five of the control cases of gynecomastia seen in adult patients without neurofibromatosis, the mammary stroma was composed of a dense fibrous tissue without remarkable features. In the remaining two cases, focal areas showing well evident pseudovascular open spaces were present. No multinucleated giant cells were present in any case.

Discussion

In the present cases, both patients showed the hallmarks of type-1 neurofibromatosis. Patient 1 had a positive family history of this condition and developed a malignant PNST at a very young age, and numerous visceral plexiform neurofibromas. Patient 2 was a 6-year-old child without known history of neurofibromatosis in his family. However, the physical examination revealed the presence of large pigmented lesions of the skin, including “inguinal freckling”, which were clinically consistent with the typical “cafè au lait spots” occurring in neurofibromatosis.

In both patients, the histological examination of the enlarged breasts revealed a marked increase of the mammary stroma, which was composed of dense, fibrous connective tissue showing slit-like pseudovascular spaces, lined by cells having a fibroblastic phenotype (expression of vimentin and CD34 antigen). All of these features appear to be consistent with the lesion named PASH by Vuitch et al. [13] and Powell et al. [11] in the female breast. In addition, the glandular component in both cases showed features suggesting a true gynecomastia (hyperplastic ducts with micropapillary projections in case 1 and presence of lobular units in case 2). Unusual features in the present cases were the presence of multinucleated giant cells lining the pseudovascular spaces and numerous mast cells throughout the mammary stroma, which are known to be increased in tissues from patients with neural disorders [10].

In women, PASH is usually seen as palpable nodules or incidental findings in routine biopsies. Less frequently, it may appear as bilateral, ill-defined breast enlargement [7, 11]. Ultrastructural and immunohistochemical studies have shown that the pseudoangiomatous spaces are due to separation of collagen fibres by cells exhibiting a fibroblastic–myofibroblastic phenotype [11, 13].

The pathogenesis of these stromal changes is unknown. However, a possible hormonal basis has been suggested because of an aberrant reactivity for progesterone receptors found in some cases [1, 11]. The role of exogenous or endogenous hormones appears supported also by the findings of similar stromal changes in two male patients in the series studied by Ibrahim et al. [7] and in 47% of the cases of gynecomastia reported by Badve and Sloane [2]. Accordingly, we found features consistent with PASH in two of the five cases of gynecomastia reviewed in patient without neurofibromatosis.

In the present cases, we are not aware of the hormonal status of the patients. However, it is noteworthy that the glandular component of the breast had features of true gynecomastia in both cases and that histological examination of the prostate in case 1 showed a moderate

degree of prostatic hyperplasia, which is very unusual in adolescent patients.

To date, PASH has not been recognised as a feature of neurofibromatosis. However, the two cases reported by Campbell [3] and by Lipper et al. [9] are very similar to the present ones. In fact, both these male patients presented a definite history of neurofibromatosis, which was associated with bilateral gynecomastia. The authors focused their attention on the presence of multinucleated giant cells immersed in a dense collagenous stroma, suggesting that a possible role of hormonal imbalance is the origin of these cells. It is noteworthy that PASH had not been described yet at the time of the case report of Lipper et al. [9] and was a very recently recognised entity when the paper by Campbell [3] was published. Nevertheless, from the description and from the microphotographs of both papers, it appears that the lesions reported are strongly reminiscent of PASH.

Giant multinucleated fibroblasts are not a finding of PASH, since they have never been recorded in the reported series of PASH in the female breast [7, 11, 13]. Badve and Sloane [2] found similar cells in only one out 93 cases of their series of male gynecomastia. Accordingly, we failed to find multinucleated cells in the five cases of gynecomastia without neurofibromatosis studied for comparison. Interestingly, the presence of giant fibroblasts lining the pseudovascular spaces is a feature somehow reminiscent of the giant cell fibroblastoma, a tumour of debated fibroblastic or neural origin [5, 14].

Althought male gynecomastia frequently shows histological features of PASH, the presence of multinucleated giant cells lining the pseudovascular spaces is probably a characteristic feature of patients with neurofibromatosis. To date, including the present cases and the cases previously reported by Campbell [3] and by Lipper et al. [9], these features have been observed in four cases of gynecomastia in patients bearing type-1 neurofibromatosis. More cases are needed to verify this phenomenon. This finding, then, might help in recognising patients with unknown von Recklinghausen's disease, presenting with gynecomastia.

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