Case Report

Giant cells in phyllodes tumour of breast: a diagnostic dilemma

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Keywords: *Phyllodes tumour, Multinucleate giant cells, Ki-67 index, Breast.*

Abstract

Phyllodes tumour (PT) accounts for 0.3-1% of all primary tumours of the breast. Classification of PT into benign, borderline and malignant types is important in determining the prognosis of the disease. Occurrence of multi-nucleate giant cells (MNGC) in PT is a rare occurrence. Two types of MNGC have been described in mammary neoplasms, the multinucleate stromal giant cells (MNSGC) and the osteoclast-like giant cells (OLGC). Of thirteen cases of Phyllodes tumour (PT) with MNGC reported till date, eleven possessed pleomorphic, bizarre-appearing MNSGC and two had bland-looking OLGC. We present a case of borderline PT with multiple foci of both MNSGC and OLGC intermixed together in a hypervascular stromal background. To the best of our knowledge, such a case has not been reported earlier. The case also highlights the dilemma in grading of PT in the presence of many pleomorphic MNSGC. In these cases, Ki-67 proliferation index is important as it is not increased in the otherwise pleomorphic and bizarre-appearing MNSGC. It is also similar to the surrounding stromal cells, implying that MNSGC do not represent a more malignant population of cells. The case details along with a brief review of literature are presented.

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Date of Submission: Aug 2, 2014 **Date of Acceptance:** Aug 31, 2014 **Date of Publishing:** Jan 28, 2015

Introduction

Phyllodes tumour (PT) accounts for 0.3-1% of all primary tumours of the breast.[1] It is classified into benign, borderline and malignant categories on the basis of nature of tumour margins, stromal cellularity, mitosis, cytologic atypia and stromal overgrowth.[1] Grading of PT is helpful in predicting the prognosis of the disease.[1]

Occurrence of multi-nucleate giant cells (MNGC) in mammary neoplasms was first highlighted in 1979 by Rosen. [2] Two types of MNGC have been described in mammary neoplasms, the multinucleate stromal giant cells (MNSGC) and the osteoclast-like giant cells (OLGC).[3-6] Occurrence of MNGC have been reported in many cases of fibroepithelial neoplasms.[3] However, only 13 cases of PT with MNGC (2 benign, 6 borderline and 5 malignant) are reported till date.[3-6] Of these, eleven cases possessed only MNSGC and two cases only OLGC. We hereby report a case of borderline PT with presence of both types of MNGC in which the pleomorphism of MNSGC also posed a difficulty in grading of the tumour.

Case Report

A 45-year-female patient presented with a painless, well defined lump measuring 3x3x3cm in the upper outer quadrant of the right breast, which was firm in consistency and freely mobile. The patient had been operated for a similar lump twice in the past at another hospital but the histopathological report was unavailable.

Fine needle aspiration cytology (FNAC) revealed highly cellular smears showing plump, round to elongated cells with moderate cytoplasm and mild to moderate nuclear pleomorphism. Many OLGCs with abundant cytoplasm containing vacuolations, stretched out branching cytoplasmic membranes and haphazardly arranged multiple round nuclei varying in number from 2-25 per giant cell were seen. Few giant cells had scant cytoplasm and overlapping hyperchromatic and bizarre nuclei that varied markedly in size. Abundant, myxoid stroma was present in the background. PT with MNGC was suggested as a provisional diagnosis and lumpectomy was advised.

Histopathological examination revealed a tumour with well-defined borders pushing into the surrounding normal breast parenchyma. The tumour was composed of epithelial and stromal elements. The epithelial component comprised of few tubular and slit-like glands lined by epithelial and myoepithelial cells. Stroma was thrown into large, leaf-like fronds (Figure 1) and was moderately cellular, composed of spindle cells showing moderate cellular pleomorphism. Focal areas of stromal overgrowth were seen. The individual spindle cells possessed oval to elongated nuclei, regular nuclear membranes, vesicular chromatin and prominent 0-2 nucleoli. Mitotic figures were 9/10hpf. Multiple foci showing bi- and multi-nucleated OLGC were appreciable at low power (10x) in areas containing many blood vessels, hemorrhage and hemosiderin laden macrophages (Figure 2). Admixed with the bland-appearing OLGC were pleomorphic MNSGC showing morphology similar to that appreciated on cytology. No inflammation/ necrosis/ granuloma formation was observed. No foreign body material was appreciated. No heterologous elements were present. Both the OLGC and MNSGC were positive for vimentin, but negative for CK, Desmin, SMA, CD34, S100 and hormone receptors, suggesting a mesenchymal origin of the MNGC. Ki-67 expression was seen in <10% of both types of MNGC and was comparable to the surrounding stromal cells. A diagnosis of borderline PT with OLGC and MNSGC was made.

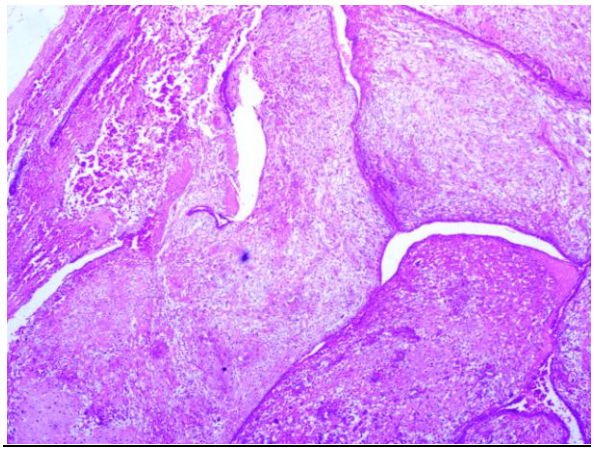

Figure 1: Phyllodes tumour, leaf like proliferation of the stroma (H&E, 4x)

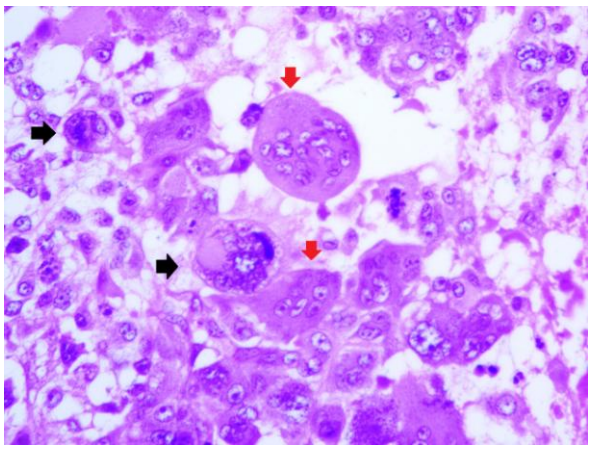

Figure 2: A focus showing closely admixed osteoclast-like giant cells (red arrows) and multi-nucleate stromal giant cells (black arrows) (H&E, 40x)

Discussion

Occurrence of MNGC in Phyllodes tumour (PT) is a rare entity.[2] Of thirteen cases of PT with MNGC reported till date, eleven possessed only MNSGC while the other two had only OLGC.[3-6] The origin and formation of both MNGCs remains unknown. MNSGC have been consistently found to be negative for epithelial and myoepithelial markers but positive for vimentin, suggesting a stromal origin.[3,4] The morphological spectrum extending from spindle shaped stromal cells, through plump mononuclear cells and finally MNSGCs, further supports a stromal origin of these cells. Tse GM *et al* reported weak positivity for actin in both stromal cells and MNSGC in 2 cases, favouring a myofibroblastic origin for MNSGC.[4] Powell CM *et al* proposed a stromal fibrohistiocytic origin of MNSGC, taking into consideration morphology and positivity for vimentin, CD34, α1- antitrypsin and α1- antichymotrypsin by immunohistochemistry.[3] The other type of MNGC i.e., OLGC are believed to be of histiocytic origin indicated by the close presence of mononuclear histiocytic cells and further supported by immunohistochemical and ultrastructural studies.[8,9] OLGC have also been reported in breast carcinoma with a hypervascular stromal background.[2,7-9]

In breast carcinoma, it is proposed that VEGF and MMP12 secretion by stromal cells leads to angiogenesis and infiltration by macrophages in stroma which later fuse to form OLGC.[9] The OLGC in the present case were also seen in close proximity to vascularised, hemorrhagic stroma. The expression of MMP12 and VEGF needs to be studied in PT with OLGC.

Although two studies comprising of 7 and 4 cases have reported MNSGC in all grades of PT,[3,4] only two cases of OLGC in PT have been reported, both in the malignant type (Table 1).[5,6] Our case showed a borderline PT with both MNSGC and OLGC, which has not been described so far to the best of our knowledge. MNSGC contain multiple, hyperchromatic nuclei arranged in linear/semicircular, florette-like/irregular pattern with inconspicuous cytoplasm.[3,4] Tse GM *et al* reported absence of mitotic activity in MNSGC.[4] Occasional MNSGC with vesicular nuclei containing clear nuclear inclusions have been described by Powell CM *et al*.[3] Most of the MNGC were noted to be randomly dispersed throughout the tumour stroma and occasionally clustered beneath the epithelium.[3] Tse GM *et al*, however, observed most of the MNSGC to be subepithelial in areas of higher stromal cellularity.[4]

TABLE 1: Summary of cases of phyllodes tumour with MNGC (1994-2014)

Reference	Age	Size	Gross	Tumour Margin	Type of lesion	Type of GC	No. of GC/10 HPF	Arrangement of nuclei in GC	Location of GC	IHC
Powell CM *et al* 1994	23-60 yrs	1.7-9 cm	Lobulated, tan grey to yellow	Well circumscribed	Benign	MNSGC	50-70	Often linear/ semicircular/ florette-like/ sometimes haphazard	-Mostly randomly dispersed -Some in subepithelial location	CK – Vim +6/9 CD68 NA CD34 +/- SMA – S100 -
				Infiltrative margin	Borderline (4 CASES)	MNSGC	<50			
				Infiltrative margin	Malignant (2 CASES)	MNSGC	0-60			
Tse GM *et al* 2001	42-50 yrs	1.8-4 cm	NA	Rounded	Benign	MNSGC	22	Linear/ florette-like/ irregular	- Subepithelial location	Vim + Des – SMA +in 2/5 CD 68 NA
				Rounded	Borderline	MNSGC	18			
				Rounded	Borderline	MNSGC	23			
				Rounded	Borderline	MNSGC	35			
				Rounded	Malignant	MNSGC	22			
Fernandez-Aquilez *et al* 2007	43 yrs	NA	NA	NA	Malignant	OLGC	NA	NA	NA	CD 68 +
Hemalatha AL *et al* 2012	30 yrs	NA	Large, grey white, lobulated	Well circumscribed	Malignant	OLGC	NA	NA	NA	CK – Vim +
Agarwal K *et al* 2014	45 yrs	2cm	Grey brown, hemorrmorrhagic, lobulated	Well circumscribed	Borderline	OLGC & MNSGC	200	Haphazard, sometimes semicircular	YES	ER/PR – CK – Vim + SMA – S 100 – CD 34 –

The occurrence of infrequent, hyperchromatic, occasionally bizarre nuclei resembling nuclei seen in symplastic uterine leiomyomas were reported by Powell CM *et al*.[3] The other type of GC, OLGC, are usually round to elongated with branching cytoplasmic processes. The cytoplasm is dense, eosinophilic with fine vacuoles.[1,7] The OLGCs are intimately associated with thin walled blood vessels and mononuclear histiocytes.[7] Only two cases of OLGC in PT have been reported so far. In a case reported by Fernandez-Aquilos *et al*,[5] benign multinucleated OLGC densely populated the sarcomatous stroma. Hemalatha AL *et al* reported a case of malignant PT possessing pleomorphic spindle cells with few uni-, bi- and multinucleated OLGC.[6]

An important aspect that needs consideration is the diagnostic dilemma caused by the presence of pleomorphic MNSGC in the grading of PT. It has been pointed out by Powell CM *et al* that the presence of MNSGC by themselves should not lead to an assessment of higher stromal cellularity or pleomorphism and therefore, alteration of the grade of PT.[3] Even presence of mitosis in MNSGC is not to be considered as evidence of malignancy.[3] Ki-67 proliferation index serves as an important marker for understanding the nature of MNSGC. Tse GM *et al* have described the low Ki-67 index of both stromal cells and MNSGC, as in the present case. It can therefore be concluded that despite the pleomorphism and bizarre appearance of MNSGC, they are no more mitotically active than the surrounding bland stromal cells and therefore upgradation of such a PT possessing MNSGC is not justifiable solely based on the pleomorphism of MNSGC.[4] In our case, MNSGC possessed overlapping, irregular nuclei of varying sizes giving a bizarre appearance to these cells which gave an overall pleomorphic appearance to the tumour and favoured a malignant PT. However the features of moderate stromal cellularity and mitosis <10/10hpf and low Ki-67 index of MNSGC favoured a borderline PT.

Another parameter that has been studied is the relationship of the number of MNGC with grade of PT. Tse GM *et al* studied 40 cases of PT, 5 of which possessed MNSGC.[4] Of these five cases, one case was benign, three were borderline and one case was malignant. The incidence of occurrence of GC in benign, borderline and malignant PT was 3.7,27 and 50% respectively. The number of giant cells ranged from 18-35 cells per 10hpf, but there was no relationship between this number and the grade of the PT.[4] The number of cases however was found to be too small for a meaningful statistical analysis by the authors.

Conclusion

To the best of our knowledge, this is the first case of borderline PT with both OLGC and MNSGC. The authors aim to highlight the diagnostic difficulties arising due to the presence of pleomorphic MNSGC in PT. The importance of Ki-67 proliferation index in GC in the assessment of grading of PT is emphasized upon.

Acknowledgements

We sincerely thank Dr Manjula Jain, Professor and Head of Department, Lady Hardinge Medical College for her constant encouragement.

Funding

None.

Competing Interests

None declared.

References

1. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, Vande Vijver MJ.WHO Classification of tumours of the breast.4th ed. Lyon. France. 2012; p 143-7.
2. Rosen PP. Multinucleate mammary stromal giant cells. A benign lesion that simulates invasive carcinoma. Cancer 1979;44:1305-8.
3. Powell CM, Cranor ML, Rosen PP. Multinucleate stromal giant cells in mammary fibroepithelial neoplasms. Arch Pathol Lab Med. 1994;118: 912-6.
4. Fernandez-Aquilos, Noel JC. Malignant Phyllodes tumour of the breast with osteoclast-like giant cells: A case report. Ann Pathol.2007;27: 31-4.
5. Hemalatha AL, Sumana Sindhuram V, Asha U. Case reports in Pathology 2012.Artcle ID 835687.
6. Cai N, Koizumi J, Vazquez M. Mammary carcinoma with osteoclast-like giant cells: a study of four cases and a review of literature. Diagn Cytopathol. 2005; 33:246–51.
7. Holland R, van Haelst UJ. Mammary carcinoma with osteoclast-like giant cells. Additional observations on six cases. Cancer.1984,53:1963-73.
8. Shishido-Hara Y, Kurata A, Fujiwara M, Itoh H , Imoto S, Kamma H. Two cases of breast carcinoma with osteoclastic giant cells: Are the osteoclastic giant cells pro-tumoural differentiation of macrophages? Diagnostic Pathology 2010;5:55.