Adenomyoepithelioma of the breast, a single-institution study of 17 cases

Dr. Casey McCusker
Student Number: 1585560

A research report in submissible format of a paper, in submission to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anatomical Pathology

Johannesburg, 2019

Declaration

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FACULTY OF HEALTH SCIENCES

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Signature of Student ..... CMcusker .....

Date 13 September 2018

Name of Primary Supervisor: Dr. Kirstin Janine Fearnhead

Signature of Primary Supervisor
..... KJF ..... **Date** 15/9/18 .....

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Article 1: Title: Adenomyoepithelioma of the breast, a single-institution study of 17 cases

Journal name, year, volume and page numbers: Human Pathology, in submission

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4th author	N/A		
5th author	N/A		
6th author	N/A		

Comments by primary supervisor:

.....
None.....

.....
.....

Letter stating role of candidate in writing paper

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13 September 2018

Letter to confirm contribution of candidate for a research report by submissible format of a paper for the degree : MMed

Dear Sir/Madam,

This letter serves to confirm my and my supervisor's contributions to submission of a paper.

I confirm that I proposed this research project and state my role in writing this paper: research proposal, ,data collection, reviewing of histopathology slides (50%), interpretation of results (80%) and writing of the manuscript (100%).

My supervisors assisted in the following:

Dr. Kirstin Fearnhead reviewed the histopathology slides (50%), assisted with interpretation of results (20%), supervised the proposal and manuscript (60%), reviewed the proposal (60%) and manuscript (80%) and assisted with compiling the report (50%). Prof. Sarah Rayne assisted with clinical information and insights (100%), supervised the proposal and manuscript (40%) and reviewed the proposal (40%) and manuscript (10%). Dr. Pamela Michelow reviewed the manuscript (10%) and assisted with compiling the report (50%).

Signed : Dr. K. Fearnhead :
Prof. S. Rayne :
Dr. P. Michelow :

Yours Sincerely,

Dr Casey McCusker :

Dedication

To Jack and Aidan.

Presentations and publications arising from this study

Presentations: none.

Publication: I intend to submit this manuscript to the journal Human Pathology.

Roles of principal investigator, supervisor and co-supervisor: Dr Casey McCusker proposed this research project, undertook data collecting, reviewing of histopathology slides and writing of the manuscript. Dr Kirstin Fearnhead reviewed the histopathology slides, assisted with interpretation of results and supervised, reviewed the proposal and manuscript and assisted with compiling the report. Professor Sarah Rayne assisted with clinical information and insights and supervised and reviewed the proposal and manuscript. Dr Pamela Michelow reviewed the manuscript and assisted with compiling the report.

Abstract

Adenomyoepitheliomas (AME) are rare tumours of the breast. Although they are benign, features such as local recurrence, malignant transformation and metastases are described. The objective is to report our findings on a case series of AME of the breast. A cross-sectional retrospective descriptive study was performed on cases with a diagnosis of AME. Clinical, radiological and histopathologic findings were studied. Seventeen cases were identified in 13 patients, with a median age of 50 years (34 to 79 years), in an 18-year time period from 2000 to 2018. The AMEs ranged in size from 1mm to 150mm. Intratumoural heterogeneity was evidenced by a combination of 2 and 3 low-power architectural patterns (solid, cystic, nodular) and high-power architectural patterns (papillary, pseudopapillary, trabecular, tubular), an admixture of subtypes (tubular, lobular and spindle cell) and myoepithelial cell phenotypes (spindle cell, plasmacytoid, epithelioid and clear cell). In summary, we present a case series of 17 cases of AME in which clinical features, radiological findings and histopathological features, including immunohistochemistry are detailed. Of note, we expand the size range and document unusual associations in 4 cases of lobular carcinoma in-situ (LCIS), necrotising granulomatous inflammation, clincial extension onto the chest wall and a rare case of AME with carcinoma (epithelial and myoepithelial carcinoma).

Acknowledgements

Dr Kirstin Fearnhead for her utmost dedication to this project, timeous reviews and invaluable knowledge.

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Dr Pamela Michelow for reviewing the manuscript and assistance with compiling this report.

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Mr Eric Liebenberg for assistance with the editing of images.

Fadila Ebrahim and Helen Nxumalo for assistance with retrieval of cases.

Table of contents

Nomenclature

AME:	Adenomyoepithelioma
ALH:	Atypical lobular hyperplasia
BI-RADS:	Breast Imaging Reporting and Data System
DCIS:	Ductal carcinoma in-situ
FNA:	Fine needle aspirate
H&E:	Haematoxylin and Eosin
CHBAH:	Chris Hani Baragwanath Academic Hospital
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
LCIS:	Lobular carcinoma in-situ
SNOMED:	Systematized Nomenclature Of Medicine
WHO:	World Health Organisation

List of figures

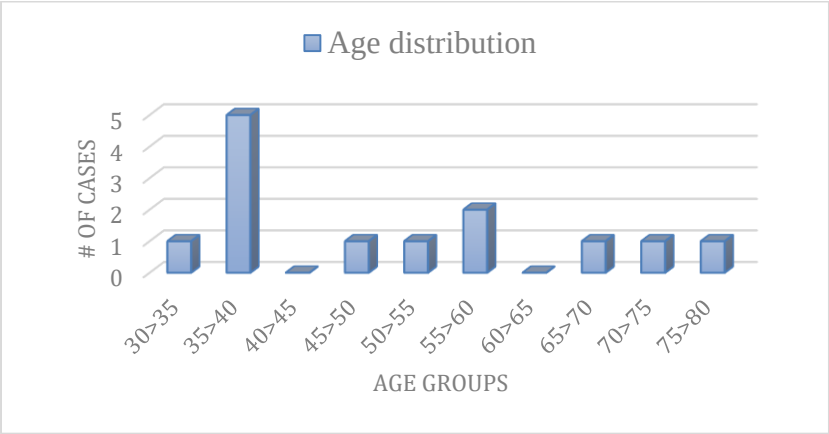

Fig. A.1 Histogram showing age distribution as number of cases per 5 year age groups in 13 patients with AME

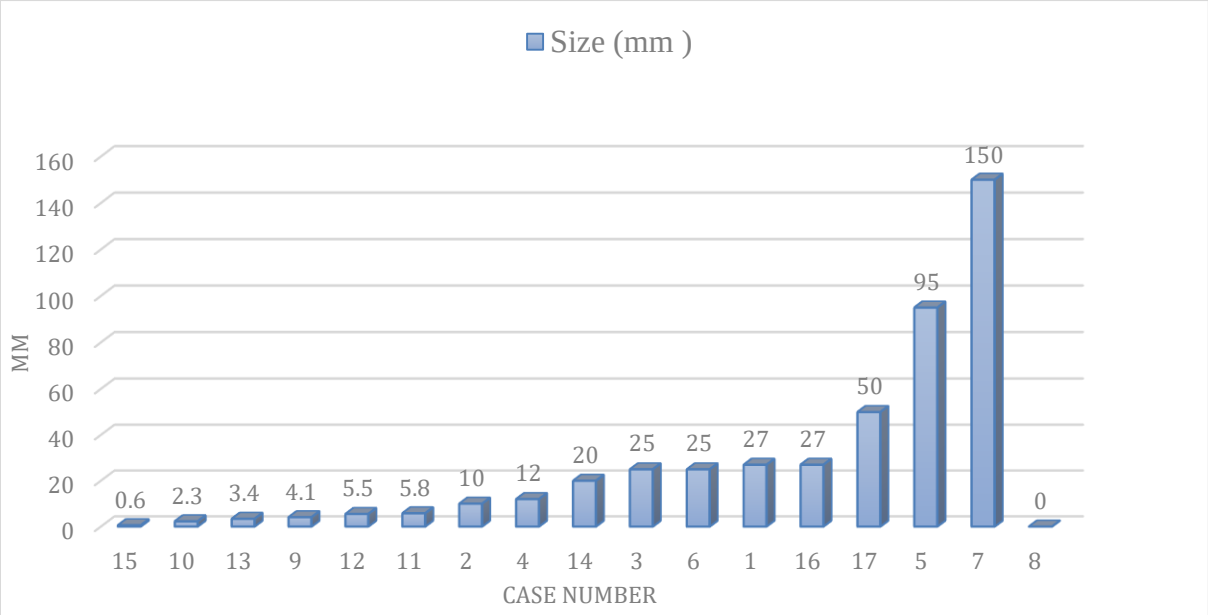

Fig. A.2 Histogram showing size of AME in each case

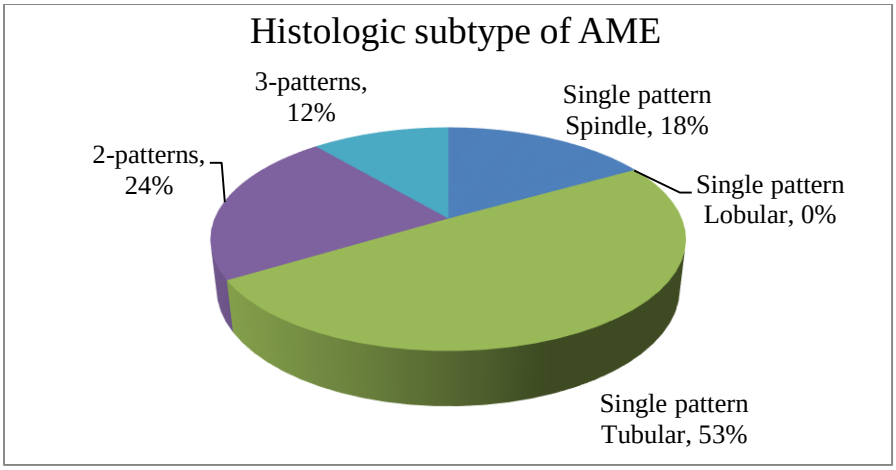

Fig. A.3 Histologic subtypes of AME with single, 2- and 3-patterns

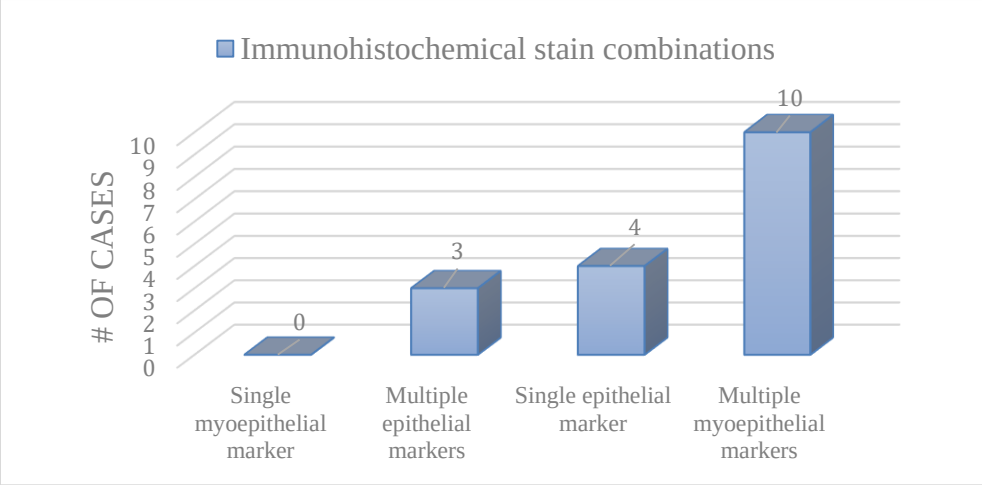

Fig. A.4 Use of single or multiple epithelial and myoepithelial immunohistochemical (IHC) stains in cases where IHC was performed

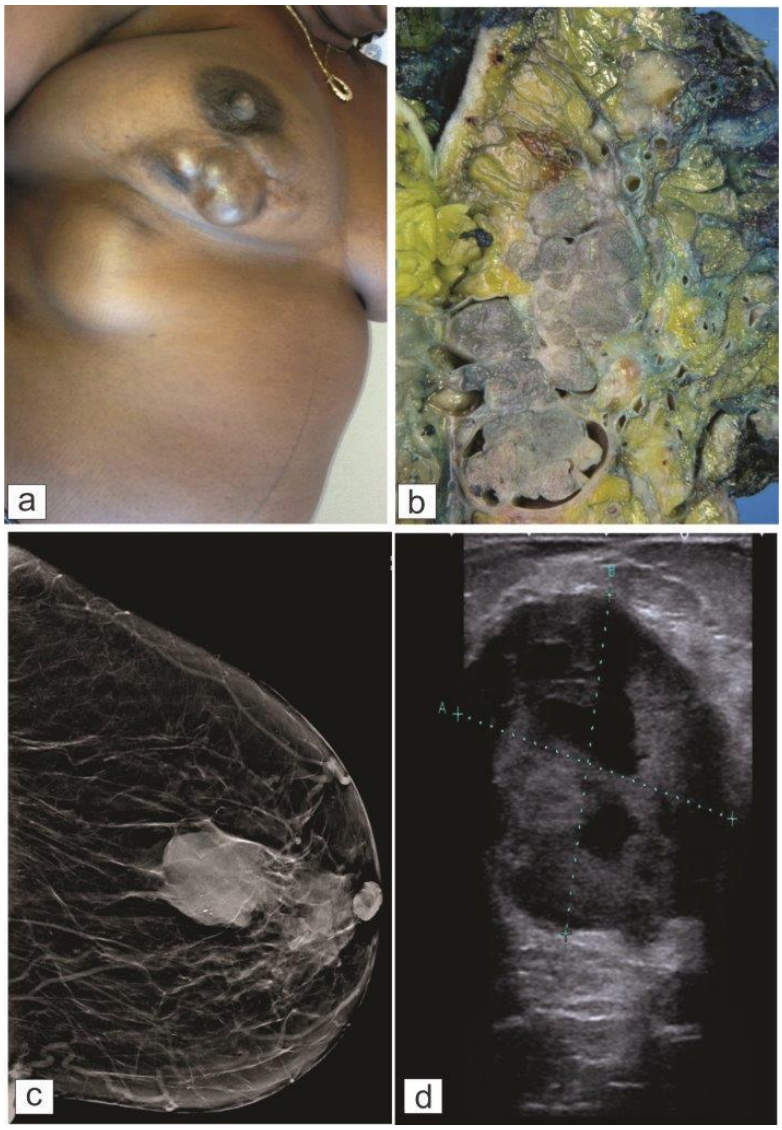

Fig. A.5 Clinical, macroscopic and radiological images of selected cases

a. Photograph of a right breast mass with clinical extension onto the chest wall 4 years following needle core biopsy (case 5).

b. Macroscopic photograph of the largest AME in our series, demonstrating solid papillary-like and cystic components (case 5) of the tumour.

c. Mammogram image of AME with carcinoma (case 17), showing a mass with ill-defined margins and calcifications, BI-RADS 5.

d. Ultrasound image of AME with carcinoma (case 17), showing an irregular solid and cystic mass.

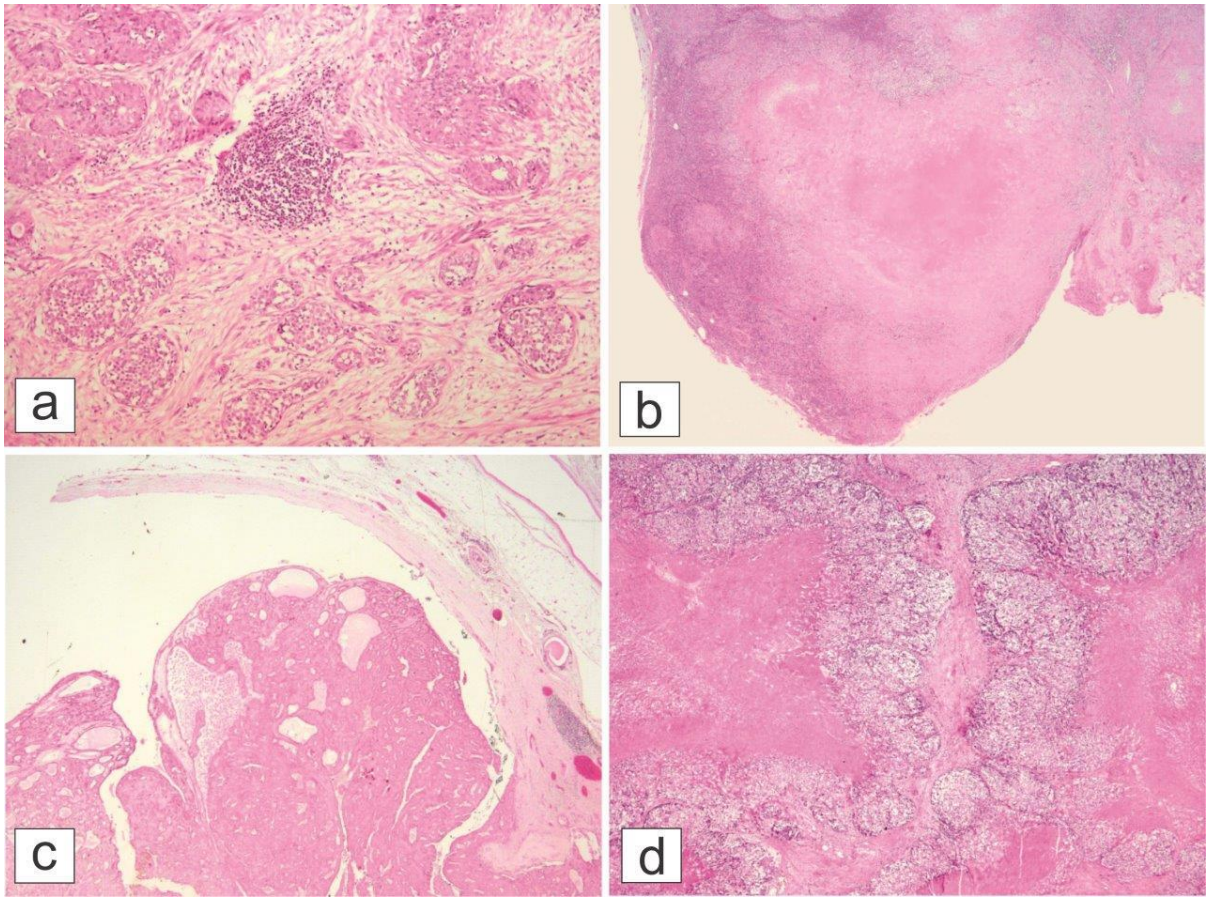

Fig. A.6 Histopathologic photomicrographs of selected cases

a. Photomicrograph showing AME with colonisation of lobules by LCIS (case 3), haematoxylin and eosin (H&E) stain, original magnification x100.
b. Photomicrograph of nodal tuberculosis in a patient with AME (case 4), H&E stain x20.
c. Photomicrograph of largest AME with cystic and papillary areas (case 5), H&E stain x20.
d. Photomicrograph of AME with carcinoma, showing malignant epithelial and myoepithelial components and extensive tumour necrosis (case 17), H&E stain x40.

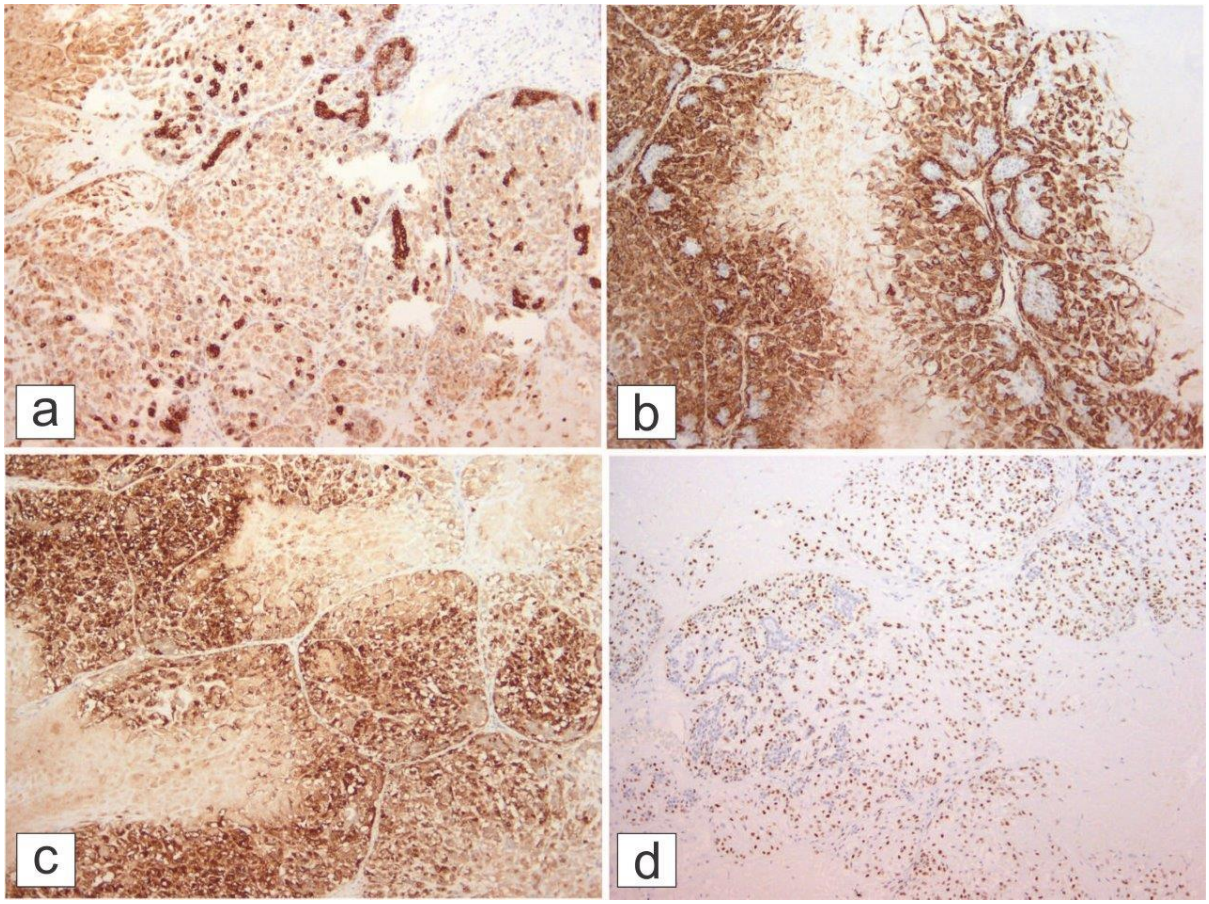

Fig. A.7 Immunohistochemical photomicrographs of selected cases

Photomicrograph of AME with carcinoma, immunohistochemical stains (case 17), original magnification x100:

a. AE1/3, showing strong-intensity positive cytoplasmic staining of the epithelial component and weak-intensity positive cytoplasmic staining of the myoepithelial component.
b. SMA, showing negative staining of the epithelial component and strong-intensity positive cytoplasmic staining of the myoepithelial component.
c. S100, showing weak positive cytoplasmic staining of the epithelial component (interpreted as negative) and strong-intensity positive cytoplasmic and nuclear staining of the myoepithelial component.
d. p63, showing negative staining of the epithelial component and strong-intensity positive nuclear staining of the myoepithelial component.

Lists of tables

Table. A.1. Adenomyoepithelioma, clinical (demographics and specimen details) and radiological (ultrasound, mammogram, and other, including BI-RADS) results

Case	Age	Laterality	Specimen	Symptoms	Episode	Size (mm)	Mammogram	Ultrasound	Other
1	58	R	NCB;WLE	Mass	Initial	27	N	N	N/A
2	38	R	LPT	Mass	Initial	20	Lobulated, cystic	Cystic, hypoechoic	N/A
3	37	R	M + ALND	Unk	Initial	25	N	N	N/A
4	35	R	LPT + LNBx	Mass	Initial	12	N	N	N/A
5	39	R	NCB;WLE	Mass onto chest wall clinically	Initial	150	N	N	N/A
6	34	L	Re-excision	None	Prev bgn phyllodes	18	N	N	MRI: fibroadenomas
7	79	L	LPT	Mass	Initial	55	N	N	N/A
8	70	L	NCB	Mass	Initial	U	Lobulated	Solid	BI-RADS 2
9-13	54	L	BBR	Macromastia	Initial	4,1;2,3;5,8;5,5;3,4	N	N	N/A
14	36	L	LPT	Unk	Initial	20	N	N	N/A
15	45	R	BBR	Macromastia	Initial	0.6	N	N	N/A
16	58	R	NCB	Mass, mastalgia	Initial	27	Lobulated	Lobulated,irreg marg, PAS	BI-RADS 4b
17	69	L	NCB;M+ALND	Mass	Initial	50	Ill-def marg, bgn calcs	Irreg solid and cystic	BI-RADS 5

Abbreviations: R: right; Unk: unknown; L: left; NCB: needle core biopsy; WLE: wide local excision; LPT: lumpectomy; M + ALND: mastectomy and axillary lymph node dissection; LNBx: lymph node biopsy; BBR: bilateral breast reduction; Prev: previous; bgn:benign; N: no report available; Ill-def: ill-defined; calcs: calcifications; Irreg: irregular; marg: margins; PAS: posterior acoustic shadowing; N/A: not applicable

Table. A.2. Adenomyoepithelioma, histopathologic and immunohistochemical (epithelial and myoepthelial) findings

Case	LP Arch	HP Arch	Subtype	Border	Myoepithelial phenotype	Margins	MF	Other features / Co-existing pathology	Immunohistochemistry*
1	So, Cy, No	Pp	Sp	Infilt	Sp, Epith	Ex	0	Seb C, FC, AM / UDH	Ep: AE1/3 +3/3; My: p63 +1/3, s100 +3/3, MSA +2/2, SMA +3/3
2	No	Tu	Tu	Infilt	Sp, Epith, CC	At	1	PC / None	Ep: AE1/3 +3/3; My: p63 +3/2, s100 +3/3, SMA +3/3, CD10 +3/3
3	So, No	Tu, Trab	Tu	Push	Sp	Ex	0	None/ LCIS, CCC, ADH	Ep: AE1/3 +3/3; My: SMA +3/3, CD10 +3/2, GFAP +3/3
4	No,	Tu, Trab	Sp	Push	Sp	Ex	0	None / MTB	None
5	So, Cy, No	Pap, Pp ,Tu	Tu, Lo	Push	Sp, CC	At	1	Infarction / None	Ep: MNF116 +3/3, Cam5.2 +3/3; My: p63 +3/2, SMA +3/3, CK5/6 +3/2, H-cal +2/3
6	Cy, No	Pp	Tu	Push	Sp, Epith	Ex	5	AM / FA, PT	Ep: none; My: p63 +3/3, s100 +3/3, CD10 +3/3.
7	So, No	Trab	Sp	Push	Sp, Epith,	At	0	Myxchndr / None	Ep: EMA +2/2, CEA +1/3; My: s100 +2/3, MSA +1/3, SMA +1/3
8	So	Trab	Tu	Unk	Epith, CC	N/A	0	None / None	Ep: EMA +3/3; My: s100 +3/3; MSA +1/2
9	So, No	Tu	Tu	Push	Sp, Epith	Ex	1	None / IDP, CS	Ep: none; My: p63 +3/3, s100 +3/3, MSA +3/3; SMA +3/3
10	No	Tu	Tu, Lo	Infilt	Sp	Ex	0	FC, AM / FA	None
11	So, No	Tu	Tu	Infilt	Sp, Epith	Ex	0	FC, AM, DC / None	None
12	No	Tu	Tu, Lo	Push	Sp	Ex	0	FC, AM / None	None
13	So, No	Pp	Tu	Infilt	Sp	Ex	0	FC, AM, DC / None	None
14	So, Cy, No	Pp, Tu	Sp, Tu	Push	Sp, CC	Ex	2	PC / None	None
15	No	Tu	Tu	Push	Sp	Ex	2	None / None	None
16	No	Tu	Tu	N/A	Sp	N/A	0	FC / CS	Ep: none; My: p63 +3/3, CK5/6 +3/3
17	No	Tu	Sp, Tu, Lo	Push	Sp, Epith, CC	Ex	10	Malignancy / CCC,ADH	Ep:AE1/3 +3/3, EMA +2/2; My: p63 +3/3, s100 +3/3, SMA +3/3, CD10 +3/3

Abbreviations: LP arch: low-power architecture; HP arch: high-power architecture; MF: mitotic figures/10 high-power field; So: solid; Cy: cystic; No: nodular; Pap: papillary; Pp: pseudopapillary, Tu: tubular; Trab: trabecular; Sp: spindle; Lo: lobular; Infilt: infiltrating; Push: pushing; Unk: unknown; N/A: not applicable; Epith: epithelioid; CC: clear cell; Ex: excised; Seb C: sebaceous cells; FC: foam cells; AM: apocrine metaplasia; UDH: usual duct hyperplasia; PC: psammomatous calcification; LCIS: lobular carcinoma in situ; CCC: columnar cell change; ADH: atypical duct hyperplasia; MTB: mycobacterial infection; FA: fibroadenoma; PT: phyllodes tumour; Myxchndr: myxochondroid; IDP: intraductal papilloma; CS: collegenous spherulosis; DC: dystrophic calcification; Ep: epithelial markers; My: myoepithelial markers; +: positive; *quantification of positive immunohistochemical result: proportion (0 = none, 1 = 1-10%, 2 = 11-50%, 3 = >50%) / intensity (0 = none, 1 = weak, 2 = moderate, 3 = strong)

Table. A.3 Frequency table illustrating clinical, radiological and histopathologic findings

	Frequency	Percentage (%		Frequency	Percentage (%)
Laterality	n=17		**Margins**	n=17	
Right	7	42	Excised	12	71
Left	10	59	At margins	3	18
Symptoms	n = 13		N/A	2	12
Mass	8	62	**Mitotic figures**	n=17	
Unknown	2	15	0-2	15	88
Macromastia	2	15	5	1	6
Mastalgia	1	8	10	1	6
Asymptomatic	1	8	**Other features**	n=17	
Mammogram findings	n=13		Absent	5	29
No report available	9	69	Present	12	70
Lobulated/cystic	1	8	Malignancy	1	6
Lobulated	2	15	**Co-existing pathology**	n=17	
Ill-defined	1	8	Absent	9	53
Ultrasound	n=13		Present	8	47
No report available	9	69	**Immunohistochemistry**	n=10	%
Cystic, solid	1	8	None	7	70
Cystic, hypoechoic	1	8	AE1/AE3	4	40
Lobulated	1	8	CAM 5.2	1	10
Irregular margins	2	15	MNF116	1	10
Posterior acoustic shadowing	1	8	EMA	3	30
Low power architecture	n=17		CEA	1	10
Single pattern	8	47	SMA	7	70
2-patterns	6	35	MSA	5	50
3-patterns	3	18	CD10	4	40
High power architecture	n=17		p63	7	70
Single pattern	13	76	GFAP	1	10
2-patterns	3	18	CK5/6	2	20
3-patterns	1	6	H-caldesmon	1	10
			S100	7	70

Table. A.4. Adenomyoepithelioma, a summary of the published case series of AME

Case series	Author	Year	Total number	Total number of AME	Recurrent	Malignant	Metastasis
1	Rosen et al [5]	1987	18	18	2	0	0
2	Decorsiere et al [6]	1988	U	17	U	U	U
3	Tavassoli [7]	1991	31	27	2	2	1
4	Loose et al [8]	1992	6	6	3	2	1
5	McClaren et al [3]	2005	35	23	0*	0	0
6	Hayes [9]	2011	25	12	2	13	4
7	Moritz [10]	2016	14	10	0	4	ND

Abbreviations: U, unknown; ND, not documented

*Only 12 of the 23 patients were followed up

Section 1: Author Guidelines

HUMAN PATHOLOGY

TABLE OF CONTENTS

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Section 2: Draft article to Human Pathology, submission for original contribution

2.1 Title page

Title:

Adenomyoepithelioma of the breast, a single-institution study of 17 cases.

Authors:

Dr. Casey Julia McCusker (MBChB)[a], Dr. Kirstin Janine Fearnhead (MBChB, FCPath (Anat), MMed)[a] and Prof. Sarah Louise Rayne (BSc, MBChB, MRCS, MMed, FCS)[b]

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Keywords:

Breast; breast tumour; adenomyoepithelioma; adenomyoepithelial carcinoma; malignant adenomyoepithelioma; malignant AME.

Conflict of interest:

None.

Financial disclosure:

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

2.2 Abstract

Adenomyoepitheliomas (AME) are rare tumours of the breast. Although they are benign, features such as local recurrence, malignant transformation and metastases are described. The objective is to report our findings on a case series of AME of the breast. A cross-sectional retrospective descriptive study was performed on cases with a diagnosis of AME. Clinical, radiological and histopathologic findings were studied. Seventeen cases were identified in 13 patients, with a median age of 50 years (34 to 79 years), in an 18 year time period from 2000 to 2018. The AMEs ranged in size from 1mm to 150mm. Intratumoural heterogeneity was evidenced by a combination of 2 and 3 low-power architectural patterns (solid, cystic, nodular) and high-power architectural patterns (papillary, pseudopapillary, trabecular, tubular), an admixture of subtypes (tubular, lobular and spindle cell) and myoepithelial cell phenotypes (spindle cell, plasmacytoid, epithelioid and clear cell). In summary, we present a case series of 17 cases of AME in which clinical features, radiological findings and histopathological features, including immunohistochemistry are detailed. Of note, we expand the size range and document unusual associations in 4 cases of lobular carcinoma in-situ (LCIS), necrotising granulomatous inflammation, clinical extension onto the chest wall and a rare case of AME with carcinoma (epithelial and myoepithelial carcinoma).

2.3 Manuscript

2.3.1. Introduction

Adenomyoepithelioma (AME) is a rare, benign biphasic tumour comprising epithelial-lined spaces surrounded by a proliferation of myoepithelial cells [1]. It was first described in the breast by Hamperl in 1970 who suggested the term AME [2]. The World Health Organisation (WHO) 2012 classifies AME of the breast as a benign epithelial-myoepithelial lesion. Malignancy may arise in an AME and the WHO further subtypes AME with carcinoma (malignant adenomyoepithelioma) according to the line of differentiation of the malignant component: luminal epithelium, myoepithelium or both (epithelial-myoepithelial carcinoma) [1]. The aim of this study is to report on a case series of AME of the breast and elucidate further characteristics of this tumour by documenting our cases of AME and comparing them to those in the literature, describing the variability in the histopathology and noting co-existing disease, including malignancy.

2.3.2 Materials and methods

2.3.2.1 Study design and study sample

A cross-sectional retrospective descriptive study took place at the Division of Anatomical Pathology of the School of Pathology at the University of the Witwatersrand, Johannesburg, South Africa. The study sample was obtained from the archives at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) and included cases from these hospitals as well as Helen Joseph Hospital, Tsepong Hospital, Kopanong Hospital and Pietersburg Hospital. Using Systematized Nomenclature of Medicine (SNOMED) codes of ‘myoepithelioma’ and ‘myoepithelial carcinoma’, as there were no SNOMED codes available for adenomyoepithelioma, a search for adenomyoepithelioma was undertaken in these search results and cases of AME of the breast from 2000 to 2018 were identified and retrieved.

2.3.2.2 Inclusion and exclusion criteria

Male and female patients, of any age, who had a histological diagnosis of AME of the breast, were included in the study. Cases with slides and/or paraffin embedded tissue blocks which were not retrievable were excluded.

2.3.2.3 Methods

Demographics (age at diagnosis, gender, laterality, type of specimen), clinical presentation (symptoms, episode and follow up if applicable) and radiological findings in terms of mammography (tumour location, margins and characteristics), ultrasound features and BI-RADS (Breast Imaging Reporting and Data System) score (1-5), were either recorded from the histopathology reports or from patient files, where possible. The available Haematoxylin and Eosin (H&E) and immunohistochemical stained slides of the cases were examined retrospectively by both investigators independently and then reviewed together. A positive immunohistochemical result was further assessed in terms of proportion and intensity (proportion was evaluated as 0 = no staining observed, 1 = 1-10%, 2 = 11-50% and 3=51-100% and intensity was evaluated as 1+ = weak, 2+ = moderate and 3+ = strong). A consensus opinion was sought if warranted. The diagnosis of AME and any concomitant pathology was reviewed critically in each case, and cases were classified histologically according to low- and high-power architectural patterns, histological subtype (as per the subtypes described to date in the literature), myoepithelial cell phenotype, tumour borders, presence or absence of increased mitotic count (defined in this study as more than 3 mitotic figures per 10 high power fields), cytologic atypia, adequacy of excision and any co-existing pathologies [1]. Permission to undertake this study was obtained from the Human Research Ethics Committee (Medical), Faculty of Health Sciences, University of the Witwatersrand in Johannesburg.

2.3.3. Results

2.3.3.1 Clinical features of AME

A total of 15 patients with a reported diagnosis of AME of the breast were identified, of which two (11%) were excluded as the review findings did not concur with the original diagnosis of AME. The final study cohort was 17 tumours in 13 patients, of which 12 had a single tumour and 1 had 5 separate and histologically distinct AMEs in the same breast. 15 tumours (88%) showed benign AME and 2 (11%) showed associated carcinoma (lobular carcinoma in-situ and AME with carcinoma. All patients were female, ranging in age from 34 to 79 years (median age, 50 years ; interquartile range, 27 years) (Fig. A.1) . The clinical, radiologic, histopathologic and immunohistochemical findings are provided in Table. A.1 and Table. A.2. A frequency table summarising certain aspects of the data is provided in Table. A.3. Furthermore, the size of the tumours (median size, 12mm ; interquartile range ,

23.25mm) and combination of histopathologic patterns present and combination of immunohistochemical markers are further qualified in Fig(s). A. 2-4, respectively.

2.3.3.2 Case reports

2.3.3.2.1 Case 3: colonisation of an AME by LCIS

- 37-year-old female.
- Right upper inner and outer quadrant breast mass.
- Needle core biopsy: lobular carcinoma in-situ.
- Mastectomy and axillary lymph node dissection: 25mm circumscribed, tan mass
- Histopathology: Fig. A.6a, AME with colonisation by extensive LCIS.
- Additional histopathologic findings: columnar cell change and atypical ductal hyperplasia.
- No invasive carcinoma or metastasis.

2.3.3.2.2 Case 4: co-existing *Mycobacterium tuberculosis* infection

- 35-year-old female, HIV-positive, pre-treatment, with pulmonary tuberculosis, on treatment for 3 months.
- Right breast nodule, 0.5cm x 0.5cm, non-tender.
- Right axillary lymphadenopathy, multiple matted lymph nodes.
- Lumpectomy and axillary lymph node dissection: Fibro-fatty breast parenchyma 12x10x7mm with no nodule macroscopically identified and lymph node 25x18x15mm with caseous necrosis on cut section.
- Histopathology: Fig. A.6b, AME in the breast and necrotising granulomatous inflammation in the lymph nodes, in keeping with *Mycobacterium tuberculosis* infection.

2.3.3.2.3 Case 5: late presentation of a large AME with chest wall extension

- 39-year-old female.
- Multinodular right breast mass with clinical extension below the inframammary fold onto the chest wall, Fig. A.5a.
- Needle core biopsy: benign proliferation of epithelial and myoepithelial cells, AME included in the differential diagnosis.
- Lost to follow-up for 4 years.
- Repeat needle core biopsy: benign neoplasm.
- Fine needle aspirate (FNA): cyst fluid with foam cells, no malignancy.
- Wide local excision: Fig. A.5b, 150mm, large, multinodular, cystic tumour with involvement of surface skin. On section, solid (firm, white, “cauliflower-like” areas) and cystic (serous and bloody fluid with clot) tumour with multiple satellite nodules.
- Microscopy: Fig. A.6c, AME with cystic degeneration. No malignancy.
- Margins involved by tumour.
- No invasive carcinoma or metastasis.
- Post-excision follow-up:
    - 1 year: mastalgia, mammogram planned. No report available.
    - 2 years: back pain localised to scapula, with pruritis and dyspnoea.
    - On examination, tenderness localised to the scar. Mammogram planned. No additional histologic specimens received.

2.3.3.2.4 Case 17: AME with carcinoma

- 69-year-old female.
- Left lower outer quadrant breast mass, BI-RADS 5.
- Needle core biopsy: invasive mammary carcinoma, triple negative molecular phenotype, metaplastic carcinoma was considered.
- Mastectomy and axillary lymph node dissection: 50mm well-circumscribed, cream-coloured tumour with surrounding haemorrhage and necrosis.
- Microscopy: Fig. A.6d, AME with carcinoma (malignant epithelial and myoepithelial components (epithelial-myoepithelial carcinoma) with residual, peripheral AME, confirmed on immunohistochemistry, Fig. A.7a-d.
- Additional histopathologic findings: intraductal papilloma, columnar cell change and atypical ductal hyperplasia.
- Margins uninvolved by tumour.

2.3.4 Discussion

In normal breast tissue and benign lesions, epithelial and myoepithelial components form the breast duct epithelium. Under neoplastic conditions, there is variation in the histologic appearance and immunophenotypic expression of myoepithelial cells, depending on whether the epithelial or myoid phenotype is expressed [2]. The combination of epithelial and myoepithelial cells can occur with considerable architectural and cytological heterogeneity within AMEs and poses diagnostic difficulty, which may be compounded by the limited representation of lesional tissue on a needle core biopsy [3, 4]. Immunohistochemical investigation is essential in order to correctly classify the lesion [4].

To the best of our knowledge, in the literature there are approximately 266 AME, 91 AME with carcinoma and 24 AME with other associated carcinoma (such as synchronous ductal carcinoma in-situ, invasvie carcinoma of no special type and invasive lobular carcinoma), the majority as individual case reports and 7 cases series (Table. A.4) [3, 5-10]. Forty-nine AME with carcinoma were reviewed and reclassified according to the WHO 2012 classification by Xu et al [11]. We contribute a large case series, of 15 AME and 2 AME with associated carcinoma, with 4 case reports highlighting noteworthy findings. Our case of AME with carcinoma can be classified according to the WHO 2012 as epithelial-myoepithelial carcinoma; this is the second most common subtype in 49 cases of malignant AME described in the literature [11].

AME typically presents as a solitary, palpable nodule of variable duration, measuring 3mm to 70mm, in mostly females aged 22-92 years (mean age of 59 years in the largest series) and our series concurs. We report 3 patients with unusual findings, including the largest and smallest AME [3, 4, 12]. Case 5, represents the largest benign AME to date, spanning a size of 150mm, with extension out of the anatomic confines of the breast and inferiorly onto the chest wall [4]. As the excision biopsy was performed 4 years following the initial diagnostic needle core biopsy, we postulate that it is due to delayed primary management that this AME reached a large size and infiltrated into adjacent structures; this underscores the worrisome behaviour sometimes encountered in AME. AME was an incidental finding in 2 patients who underwent bilateral breast reductions for macromastia, 1 having a single AME, measuring 1mm (the smallest in the literature to date), and the other having 5 completely separate benign AMEs in the same breast. Han and Peng address multicentric AME in a report of a patient with 1 benign AME, 1 atypical AME and 1 AME with DCIS in the same breast [13]. When comparing our case of AME with carcinoma (case 17) to those reviewed by Xu et al.,

our case, with a maximum diameter of 50mm is less than the maximum size of up to 170mm [11].

Radiological findings were available for 6 of 17 cases and are listed, along with the clinical findings, in Table. A.1. The mammogram and ultrasound images of the AME with carcinoma are present in Fig. A.5c and Fig. A.5d, respectively. The mammography and ultrasound findings of the remaining 5 AMEs with available imaging were consistent with what is described in the literature. Mammography reveals a dense, round to lobulated, often circumscribed (but sometimes ill-defined) mass, resembling a fibroadenoma, occasionally having a cystic appearance [4, 8, 14, 15]. Calcifications are regarded as a suspicious finding when seen on imaging, but are rare, and were not seen in our series [16]. Ultrasound reveals a round or oval, solid mass with a hypoechoic or complex echogenic texture and posterior or combined acoustic enhancement, which indicate the nature of the cellular composition of the tumour) [9, 12, 17, 18]. Two of our benign AME cases were accorded a BI-RADS score: one of 2 and the other of 4b. A BI-RADS 2 score correlates with benign findings and a BI-RADS 4b assessment is indeterminate, meaning radiologically, there were no 'suspicious for' or 'highly suggestive' of features of malignacy in our benign AMEs.

The well-described wide range in appearance of AME on low-power architecture (solid, cystic, nodular), high-power architecture (papillary, pseudopapillary, trabecular and tubular), variable morphologic subtypes (tubular, lobular and spindle) (summarised in Figure. A.3) and diverse appearance of the myoepithelial cells (spindle, clear cell, epithelioid, plasmacytoid) were present in our case series (Table. A.2) [4, 6, 12]. In our study, similar to the findings of Tavassoli, a preponderance of a tubular pattern was found [7]. Other pathologic features including focal metaplastic change, a sebaceous cell population, myxochondroid background and apocrine metaplasia were infrequent findings in our series. Foam cells were identified, a finding which has been described in FNA series, and in a single case report on histopathology of AME with squamous and sebaceous metaplasia [6, 8, 9, 13]. On microscopy, our AME with carcinoma is consistent with most cases in the series by Xu et al, showing cytological atypia in both epithelial and myoepithelial components, necrosis and a mitotic count of 10 per 10 high-power fields [11].

Regarding immunohistochemistry, a panel approach which confirms the dual phenotype of AME is advised [4]. Although none of our cases used the same combination of immunohistochemical stains, the presence of both components was confirmed (Table. A.2). The number of cases using a single and/or multiple epithelial and myoepithelial markers is

demonstrated in Figure. A.4. As described in the literature, staining of the epithelial cells with cytokeratin, epithelial lumen with EMA and staining of myoepithelial component with the following markers: p63, 34βE12, CK5/6, CK14, CD10 and actins (smooth muscle actin and muscle specific actin), highlights the tumour's biphasic nature. S100 may mark-both components [3, 4, 19]. Regarding the hormonal profile, oestrogen receptor and progesterone receptor may show weak, patchy positive staining and HER2 is negative. The Ki-67 proliferation index is moderate and is commonly higher in the myoepithelial component [1].

An association between AME and pulmonary *Mycobacterium tuberculosis* infection was made in a case report of bilateral AME in a young female patient, attributed to immunosuppression following treatment with Imatinib [20]. Case 4 illustrates an HIV positive female with an AME that presented as a breast nodule and lymphadenopathy. The clinical differential diagnosis of the latter included tuberculous lymphadenitis and lymphoma. Nodal tuberculosis was confirmed on histopathology and is attributed to the patient's immunosuppressed state.

Co-existing AME and phyllodes tumour is exceedingly rare: 1 case reports AME and benign phyllodes in the same tumour and 1 case reports separate malignant AME and malignant phyllodes in the same breast [9, 21]. Case 6 describes a patient who underwent re-excision of a benign phyllodes tumour, and the re-excision specimen showed an AME, along with multiple fibroadenomas.

Lobular neoplasia and AME have been infrequently documented [8, 22, 23]. Hayes listed a case of AME and lobular carcinoma in-situ (LCIS)/atypical lobular hyperplasia (ALH) in a case series, which to our knowledge is the only other case of co-existing AME and LCIS [9]. Zhang reported AME and co-existing ALH and provided diagnostic clues for accurate diagnosis with resultant management implications [22]. Our case (case 3) adds to the literature another AME with associated lobular neoplasia. Association with ductal carcinoma in-situ (DCIS) and invasive carcinoma of no special type is more frequently reported, however none of our cases showed either association [8, 9, 13, 24-26].

Axillary lymph node metastasis of both AME and AME with carcinoma, of either epithelial, myoepithelial or both components, has been described but was not documented in our series [6, 8, 27] however this is a limitation of our study as lymph nodes were submitted in 2 out of 17 (12%) cases. Distant metastasis of AME with carcinoma is by haematogenous spread and sites include lung, liver, bone, thyroid, kidney, thoracic wall and brain [11, 12].

Simple excision of most AME is curative and the recommended treatment of AME with carcinoma is wide local excision with adequate margins [6, 12]. Local recurrence has been reported and may be attributed to multinodular growth, intraductal extension of a lesion or incomplete excision [8]. Our study was limited by a lack of follow-up information and we would further benefit from this clinical correlation. As AME was present at margins in 2 cases, follow-up specifically with regards to recurrence would be valuable. The long-term follow-up for our patient of AME with carcinoma is still to be determined.

2.3.5. Conclusion

In summary, we present 17 cases of AME and emphasize the histological heterogeneity of AME, which may cause diagnostic confusion, and reiterate the value of an immunohistochemical panel including myoepithelial and epithelial markers in avoiding misdiagnosis.

2.3.6 Acknowledgements

Prof Mario Altini for assistance with initiating this report, Dr Pamela Michelow for reviewing the manuscript, Dr Sarah Nietz, consultant surgeon and Dr Jackie Smilg, consultant radiologist at the Breast Imaging Unit at CMJAH, histopathologists Dr Zama Mtshali (CMJAH) and Dr Aubrey Madliwa (Lancet Laboratories) for contributing the AME with carcinoma; histopathologist Dr Sugeshnee Pather (CHBAH) for the cases of AME contributed from this hospital, Mr Eric Liebenberg for assistance with the images and Fadila Ebrahim and Helen Nxumalo for assistance with retrieval of cases.

2.4 Lists of tables and figures

2.4.1 List of tables

Table. A.1. Adenomyoepithelioma, clinical (demographics and specimen details) and radiological (ultrasound, mammogram, and other, including BI-RADS) results.

Case	Age	Laterality	Specimen	Symptoms	Episode	Size (mm)	Mammogram	Ultrasound	Other
1	58	R	NCB;WLE	Mass	Initial	27	N	N	N/A
2	38	R	LPT	Mass	Initial	20	Lobulated, cystic	Cystic, hypoechoic	N/A
3	37	R	M + ALND	Unk	Initial	25	N	N	N/A
4	35	R	LPT + LNBx	Mass	Initial	12	N	N	N/A
5	39	R	NCB;WLE	Mass onto chest wall clinically	Initial	150	N	N	N/A
6	34	L	Re-excision	None	Prev bgn phyllodes	18	N	N	MRI: fibroadenomas
7	79	L	LPT	Mass	Initial	55	N	N	N/A
8	70	L	NCB	Mass	Initial	U	Lobulated	Solid	BI-RADS 2
9-13	54	L	BBR	Macromastia	Initial	4,1;2,3;5,8;5,5;3,4	N	N	N/A
14	36	L	LPT	Unk	Initial	20	N	N	N/A
15	45	R	BBR	Macromastia	Initial	0.6	N	N	N/A
16	58	R	NCB	Mass, mastalgia	Initial	27	Lobulated	Lobulated,irreg marg, PAS	BI-RADS 4b
17	69	L	NCB;M+ALND	Mass	Initial	50	Ill-def marg, bgn calcs	Irreg solid and cystic	BI-RADS 5

Abbreviations: R: right; Unk: unknown; L: left; NCB: needle core biopsy; WLE: wide local excision; LPT: lumpectomy; M + ALND: mastectomy and axillary lymph node dissection; LNBx: lymph node biopsy; BBR: bilateral breast reduction; Prev: previous; bgn:benign; N: no report available; Ill-def: ill-defined; calcs: calcifications; Irreg: irregular; marg: margins; PAS: posterior acoustic shadowing; N/A: not applicable

Table. A.2. Adenomyoepithelioma, histopathologic and immunohistochemical (epithelial and myoepthelial) findings.

Case	LP Arch	HP Arch	Subtype	Border	Myoepithelial phenotype	Margins	MF	Other features / Co-existing pathology	Immunohistochemistry*
1	So, Cy, No	Pp	Sp	Infilt	Sp, Epith	Ex	0	Seb C, FC, AM / UDH	Ep: AE1/3 +3/3; My: p63 +1/3, s100 +3/3, MSA +2/2, SMA +3/3
2	No	Tu	Tu	Infilt	Sp, Epith, CC	At	1	PC / None	Ep: AE1/3 +3/3; My: p63 +3/2, s100 +3/3, SMA +3/3, CD10 +3/3
3	So, No	Tu, Trab	Tu	Push	Sp	Ex	0	None /LCIS, CCC, ADH	Ep: AE1/3 +3/3; My: SMA +3/3, CD10 +3/2, GFAP +3/3
4	No,	Tu, Trab	Sp	Push	Sp	Ex	0	None / MTB	None
5	So, Cy, No	Pap, Pp ,Tu	Tu, Lo	Push	Sp, CC	At	1	Infarction / None	Ep: MNF116 +3/3, Cam5.2 +3/3; My: p63 +3/2, SMA +3/3, CK5/6 +3/2, H-cal +2/3
6	Cy, No	Pp	Tu	Push	Sp, Epith	Ex	5	AM / FA, PT	Ep: none; My: p63 +3/3, s100 +3/3, CD10 +3/3.
7	So, No	Trab	Sp	Push	Sp, Epith,	At	0	Myxchndr / None	Ep: EMA +2/2, CEA +1/3; My: s100 +2/3, MSA +1/3, SMA +1/3
8	So	Trab	Tu	Unk	Epith, CC	N/A	0	None / None	Ep: EMA +3/3; My: s100 +3/3; MSA +1/2
9	So, No	Tu	Tu	Push	Sp, Epith	Ex	1	None / IDP, CS	Ep: none; My: p63 +3/3, s100 +3/3, MSA +3/3; SMA +3/3
10	No	Tu	Tu, Lo	Infilt	Sp	Ex	0	FC, AM / FA	None
11	So, No	Tu	Tu	Infilt	Sp, Epith	Ex	0	FC, AM, DC / None	None
12	No	Tu	Tu, Lo	Push	Sp	Ex	0	FC, AM / None	None
13	So, No	Pp	Tu	Infilt	Sp	Ex	0	FC, AM, DC / None	None
14	So, Cy, No	Pp, Tu	Sp, Tu	Push	Sp, CC	Ex	2	PC / None	None
15	No	Tu	Tu	Push	Sp	Ex	2	None / None	Ep: none; My: None
16	No	Tu	Tu	N/A	Sp	N/A	0	FC / CS	Ep: none; My: p63 +3/3, CK5/6 +3/3
17	No	Tu	Sp, Tu, Lo	Push	Sp, Epith, CC	Ex	10	Malignancy /CCC,ADH	Ep:AE1/3 +3/3, EMA +2/2; My: p63 +3/3, s100 +3/3, SMA +3/3, CD10 +3/3

Abbreviations: LP arch: low-power architecture; HP arch: high-power architecture; MF: mitotic figures/10 high-power field; So: solid; Cy: cystic; No: nodular; Pap: papillary; Pp: pseudopapillary, Tu: tubular; Trab: trabecular; Sp: spindle; Lo: lobular; Infilt: infiltrating; Push: pushing; Unk: unknown; N/A: not applicable; Epith: epithelioid; CC: clear cell; Ex: excised; Seb C: sebaceous cells; FC: foam cells; AM: apocrine metaplasia; PC: psamommatous calcification; LCIS: lobular carcinoma in situ; CCC: columnar cell change; ADH: atypical duct hyperplasia; MTB: mycobacterial infection; FA: fibroadenoma; PT: phyllodes tumour; Myxchndr: myxochondroid; IDP: intraductal papilloma; CS: collegenous spherulosis; DC: dystrophic calcification; Ep: epithelial markers; My: myoepithelial markers; +: positive; *quantification of positive immunohistochemical result: proportion (0 = none, 1 = 1-10%, 2 = 11-50%, 3 = >50%) / intensity (0 = none, 1 = weak, 2 = moderate, 3 = strong).

Table. A.3 Frequency table illustrating clinical, radiological and histopathologic findings

	Frequency	Percentage		Frequency	Percentage
Laterality	n=17		**Margins**	n=17	
Right	7	42	Excised	12	71
Left	10	59	At margins	3	18
Symptoms	n = 13		N/A	2	12
Mass	8	62	**Mitotic figures**	n=17	
Unknown	2	15	0-2	15	88
Macromastia	2	15	5	1	6
Mastalgia	1	8	10	1	6
Asymptomatic	1	8	**Other features**	n=17	
Mammogram findings	n=13		Absent	5	29
No report available	9	69	Present	12	70
Lobulated/cystic	1	8	Malignancy	1	6
Lobulated	2	15	**Co-existing pathology**	n=17	
Ill-defined	1	8	Absent	9	53
Ultrasound	n=13		Present	8	47
No report available	9	69	**Immunohistochemistry**	n=10	%
Cystic, solid	1	8	None	7	70
Cystic, hypoechoic	1	8	AE1/AE3	4	40
Lobulated	1	8	CAM 5.2	1	10
Irregular margins	2	15	MNF116	1	10
Posterior acoustic shadowing	1	8	EMA	3	30
Low power architecture	n=17		CEA	1	10
Single pattern	8	47	SMA	7	70
2-patterns	6	35	MSA	5	50
3-patterns	3	18	CD10	4	40
High power architecture	n=17		p63	7	70
Single pattern	13	76	GFAP	1	10
2-patterns	3	18	CK5/6	2	20
3-patterns	1	6	H-caldesmon	1	10
			S100	7	70

Table. A.4. Adenomyoepithelioma, a summary of the published case series of AME.

Case series	Author	Year	Total number	Total number of AME	Recurrent	Malignant	Metastasis
1	Rosen et al [5]	1987	18	18	2	0	0
2	Decorsiere et al [6]	1988	U	17	U	U	U
3	Tavassoli [7]	1991	31	27	2	2	1
4	Loose et al [8]	1992	6	6	3	2	1
5	McClaren et al [3]	2005	35	23	0*	0	0
6	Hayes [9]	2011	25	12	2	13	4
7	Moritz [10]	2016	14	10	0	4	ND

Abbreviations: U, unknown; ND, not documented

*Only 12 of the 23 patients were followed up

2.4.2 List of figures with captions

Fig. A.1 Histogram showing age distribution as number of cases per 5 year age groups in 13 patients with AME

Fig. A.2 Histogram showing size of AME in each case Fig. A.3 Histologic subtypes of AME with single, 2- and 3-patterns

Fig. A.4 Use of single or multiple epithelial and myoepithelial immunohistochemical (IHC) stains in cases where IHC was performed

Fig. A.5. Clinical, macroscopic and radiological images of selected cases

a. Photograph of a right breast mass with clinical extension onto the chest wall 4 years following needle core biopsy (case 7).
b. Macroscopic photograph of the largest AME in our series, demonstrating solid and cystic components (case 7) of the tumour.
c. Mammogram image of AME with carcinoma (case 17), showing a mass with ill-defined margins and calcifications, BI-RADS 5.
d. Ultrasound image of AME with carcinoma (case 17), showing an irregular solid and cystic mass.

Fig. A.6. Histopathologic photomicrographs of selected cases

a. Photomicrograph showing AME with colonisation of lobules by LCIS (case 3), haematoxylin and eosin (H&E) stain, original magnification x100.
b. Photomicrograph of nodal tuberculosis in a patient with AME (case 4), H&E stain x20.
c. Photomicrograph of largest AME with cystic and papillary areas (case 7), H&E stain x20.
d. Photomicrograph of AME with carcinoma, showing malignant epithelial and myoepithelial components and extensive tumour necrosis (case 17), H&E stain x40.

Fig. A.7. Immunohistochemical photomicrographs of selected cases

Photomicrograph of AME with carcinoma, immunohistochemical stains (case 17), original magnification x100:

a. AE1/3, showing strong-intensity positive cytoplasmic staining of the epithelial component and weak-intensity positive cytoplasmic staining of the myoepithelial component.
b. SMA, showing negative staining of the epithelial component and strong-intensity positive cytoplasmic staining of the myoepithelial component.
c. S100, showing , showing weak positive cytoplasmic staining (interpreted as negative) and strong-intensity positive cytoplasmic and nuclear staining of the myoepithelial component.
d. p63, showing negative staining of the epithelial component and strong-intensity positive nuclear staining of the myoepithelial component.

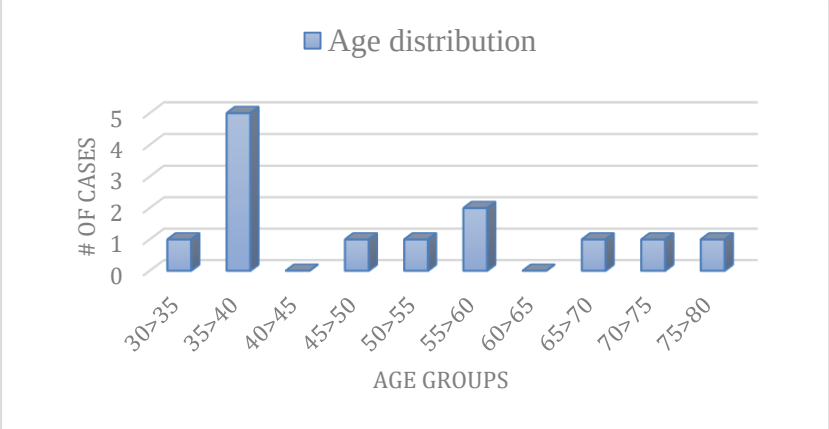

Fig. A.1 Histogram showing age distribution as number of cases per 5 year age groups in 13 patients with AME

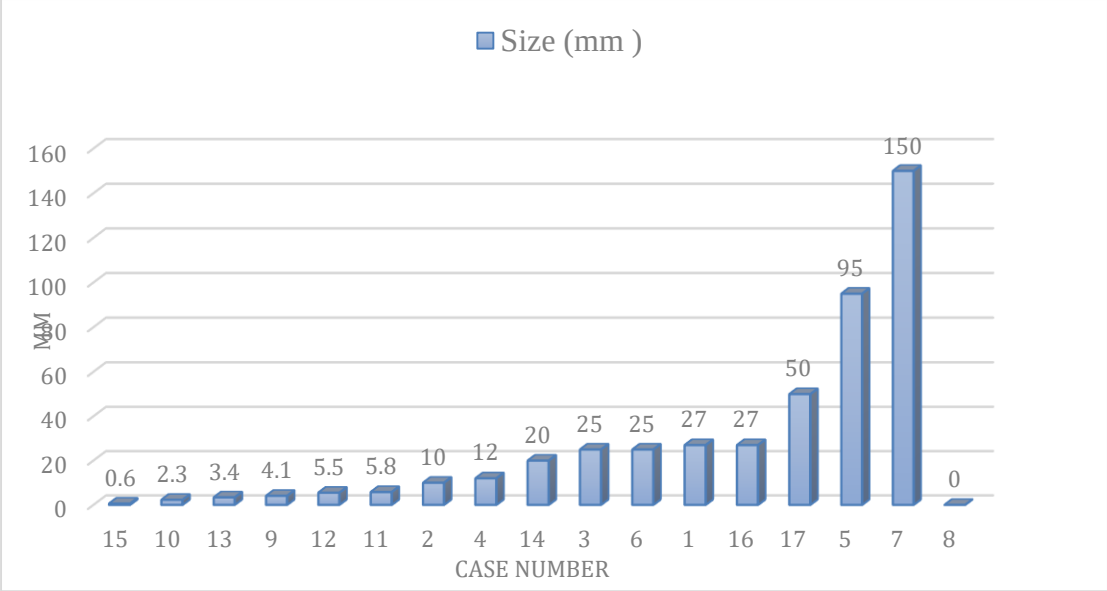

Fig. A.2 Histogram showing size of AME in each case

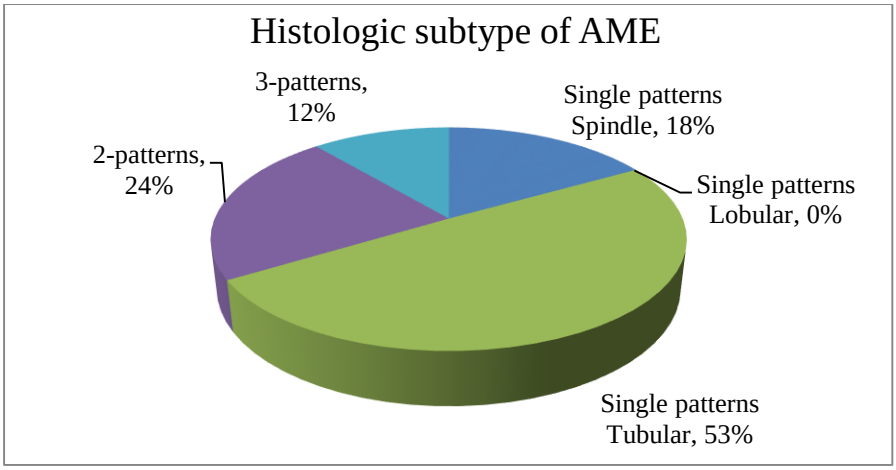

Fig. A.3 Histologic subtypes of AME with single, 2- and 3-patterns

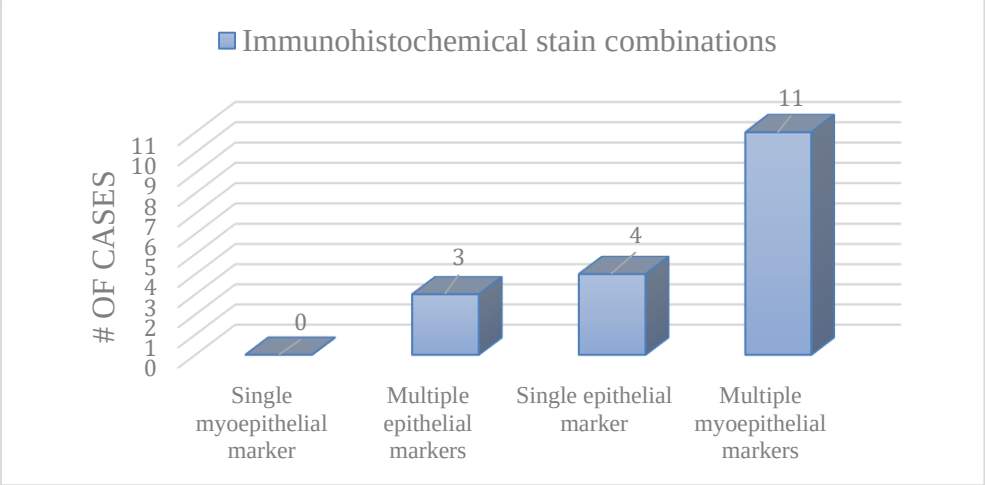

Fig. A.4 Use of single or multiple epithelial and myoepithelial immunohistochemical (IHC) stains in cases where IHC was performed

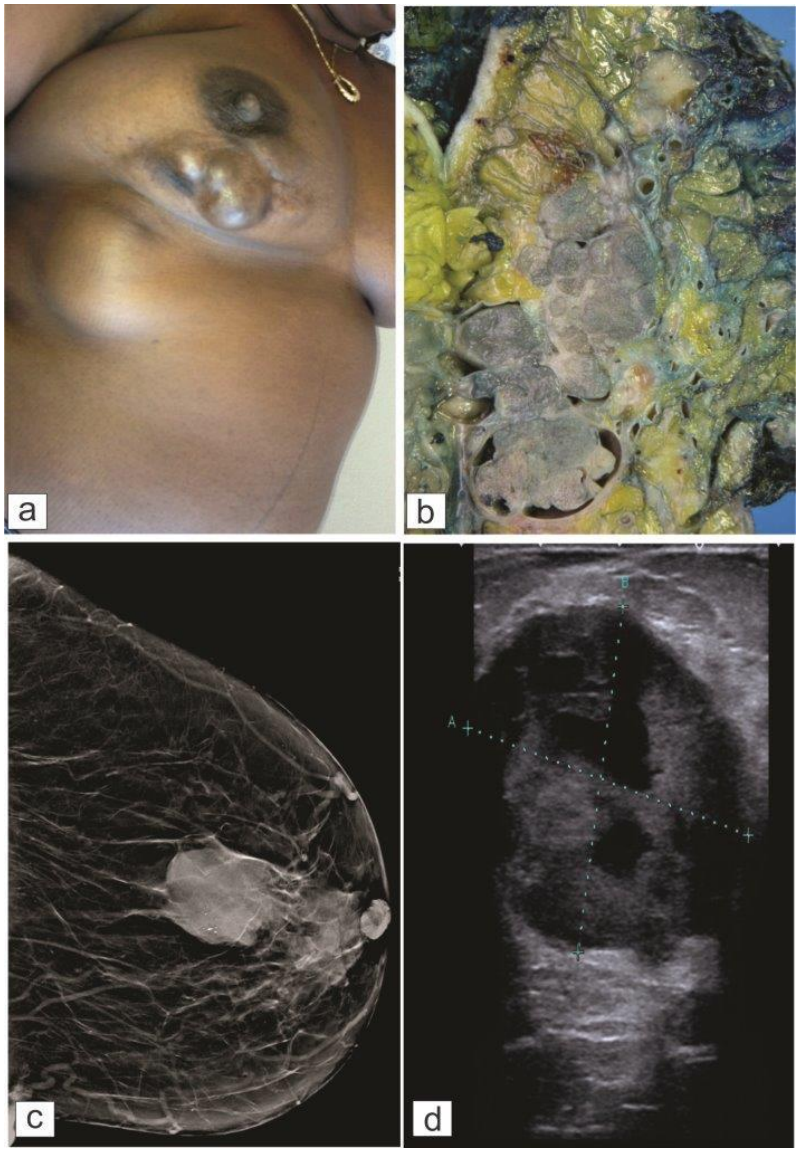

Fig. A.5 Clinical, macroscopic and radiological imgaes of selected cases

a. Photograph of a right breast mass with clinical extension onto the chest wall 4 years following needle core biopsy (case 5).
b. Macroscopic photograph of the largest AME in our series, demonstrating solid (papillary-like) and cystic components (case 5) of the tumour.
c. Mammogram image of AME with carcinoma (case 17), showing a mass with ill-defined margins and calcifications, BI-RADS 5.
d. Ultrasound image of AME with carcinoma (case 17), showing an irregular solid and cystic mass.

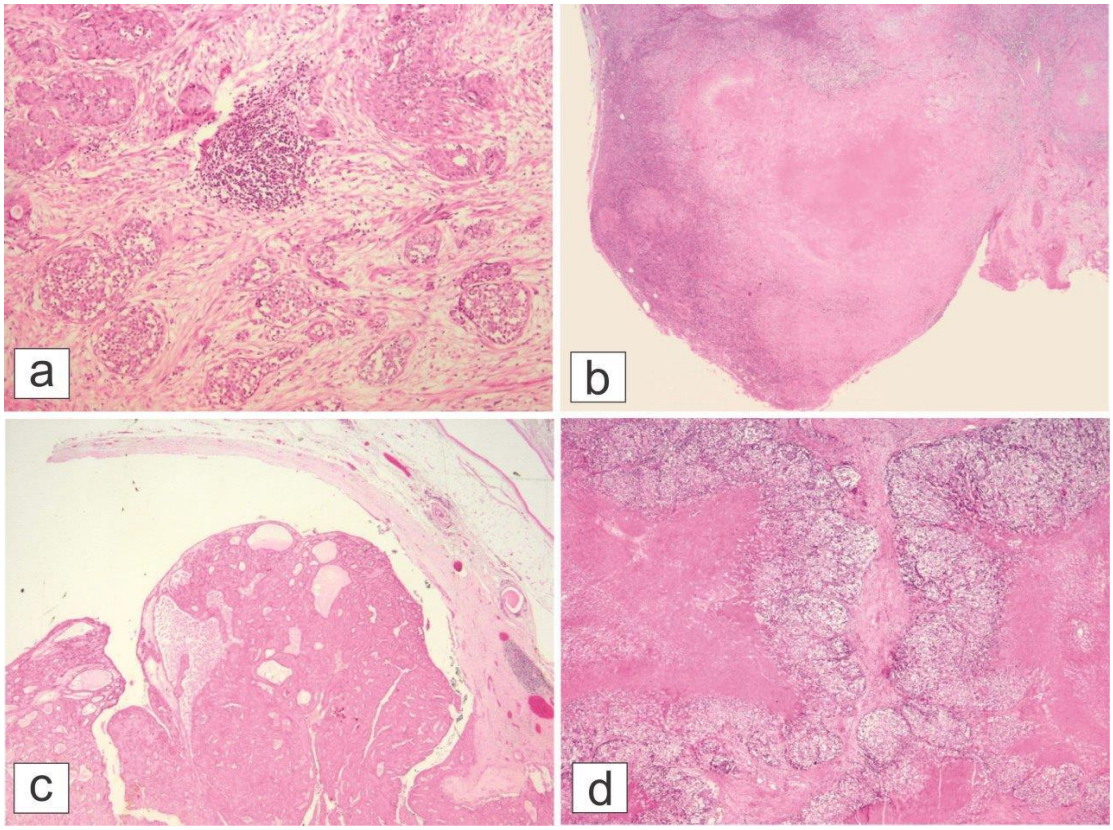

Fig. A.6 Histopathologic photomicrographs of selected cases

a. Photomicrograph showing AME with colonisation of lobules by LCIS (case 3), haematoxylin and eosin (H&E) stain, original magnification x100.
b. Photomicrograph of nodal tuberculosis in a patient with AME (case 4), H&E stain x20.
c. Photomicrograph of largest AME with cystic and papillary areas (case 5), H&E stain x20.
d. Photomicrograph of AME with carcinoma, showing malignant epithelial and myoepithelial components and extensive tumour necrosis, (case 17), H&E stain x40.

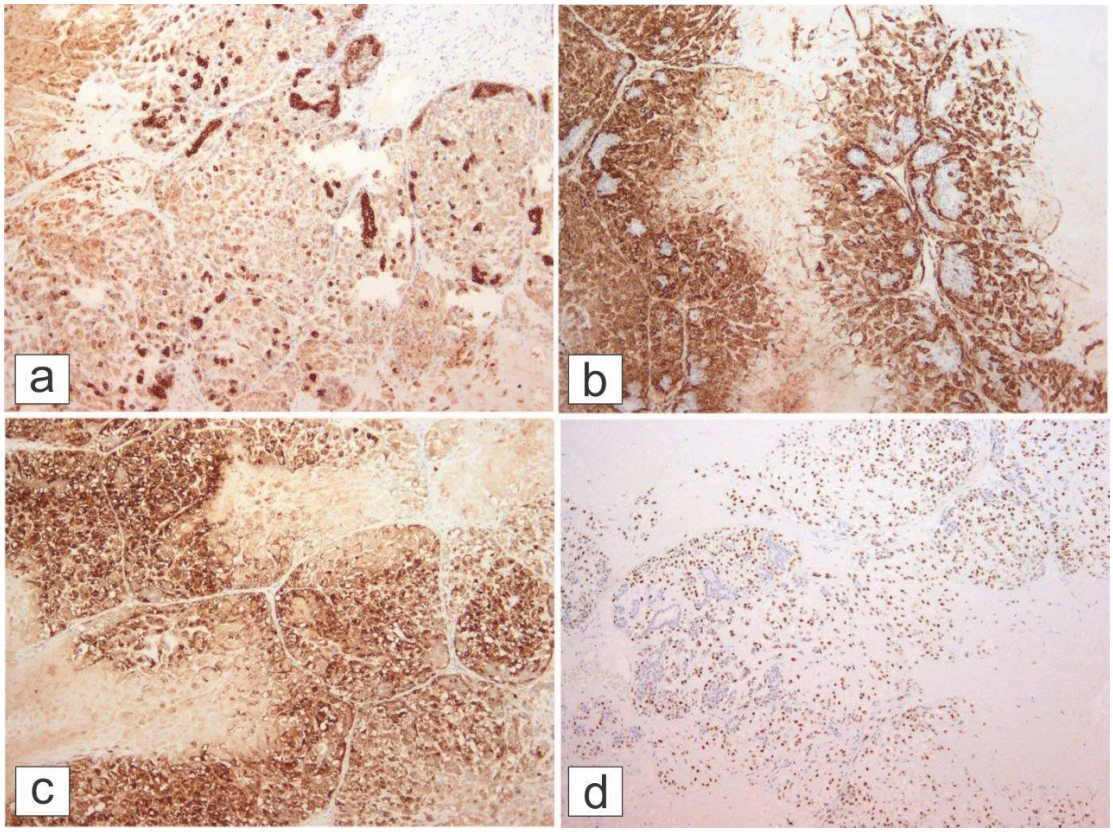

Fig. A.7 Immunohistochemical photomicrographs of selected cases

Photomicrograph of AME with carcinoma, immunohistochemical stains (case 17), original magnification x100:

a. AE1/3, showing positive strong-intensity positive cytoplasmic staining of the epithelial component and weak-intensity positive cytoplasmic staining of the myoepithelial component.
b. SMA, showing negative staining of the epithelial component and strong-intensity positive cytoplasmic staining of the myoepithelial component.
c. S100, showing , showing weak positive cytoplasmic staining and negative nuclear staining of the epithelial component (interpreted as negative) and strong-intensity positive cytoplasmic and nuclear staining of the myoepithelial component.
d. p63, showing negative staining of the epithelial component and strong-intensity positive nuclear staining of the myoepithelial component

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Section 3: Appendices

3.1 Ethics approval

R14/49 Dr Casey Julia McCusker and Dr Sarah Rayne

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170291

NAME: (Principal Investigator)	Dr Casey Julia McCusker and Dr Sarah Rayne
DEPARTMENT:	Anatomical Pathology Faculty of Health Sciences University of the Witwatersrand Medical School
PROJECT TITLE:	Adenomyoepithelioma of the Breast: Case Series
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study (M150884)
SUPERVISOR:	Dr Kirstin Janine Fearnhead
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

3.2 Ethics amendment approval letter

Division of Anatomical Pathology

3rd Floor

Faculty of Health Sciences

University of the Witwatersrand

7 York Road, Parktown

2193

28 February 2018

Dear Professor Cleaton-Jones,

I wish to amend my MMed protocol as follows, pertaining to methods (section 4):

A. 4.6 In addition, a review of patient's clinical files will be undertaken, where possible.
B. 4.3 Time period : year of study extended from March 2016 to March 2017.

Please find attached an updated version of my protocol. This does not affect my research tools, however the data sheet has been included for completeness sake. In addition, please find prior letter of approval/ethics clearance.

Kind regards,

Casey McCusker

Registrar, Anatomical Pathology, NHLS/WITS

3.3 Postgraduate assessor group approval

University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
ASSESSORS MEETING

1585560

CANDIDATE: C. McCusker

Date of Assessor Group Meeting: 14th Sept. 2016 School / Department / Division: Pathology

(Yes) No Is the research question clearly identified and described?

Comments:

(Yes) No Not entirely

Is the design of the study and methods the methods used appropriate for the research question being asked?

Comments:
- ~~Aims~~ 11 cases have already been identified
- check typos
- put sub-headings in Introduction
- Submit others

Is the study feasible within:

i. the applicant's resources? (Yes) No

ii. the departments resources? (Yes) No

iii. the time frame? (Yes) No

3.4 Postgraduate assessor group approval corrections

4 October 2016

Dear Drs Fearnhead and Rayne,

RE : AMENDMENTS TO MMED (ANAT PATH) RESEARCH PROTOCOL FOLLOWING SCHOOL OF PATHOLOGY ASSESSORS MEETING

The following amendments were made to my MMed (ANAT PATH) Research Protocol following the assessors meeting on 14/09/2016:

1. Spelling errors:

   i. immunphenotypic amended to immunophenotypic
   Page 2, 2nd paragraph, line

   ii. myopeithelial amended to myoepithelial
   Page 3, last paragraph, 3rd line

   iii. epithelial-myoepithelail amended to epithelial-myoepithelial
   Page 9 , Reference 1

2. Headings added to the introduction, as follows:

   i. a) Clinical presentation
   Page 3, 3rd paragraph

   ii. b) Radiologic features
   Page 3, 4rd paragraph

   iii. c) Gross pathologic features
   Page 3, 3rd paragraph

   iv. d) Microscopic pathologic features

   Page 4, 1st paragraph

v. e) Immunohistochemistry

Page 5, 1st paragraph

vi. f) Differential diagnosis

Page 5, 5th paragraph

vii. g) Biologic behaviour and treatment

Page 6, 2nd paragraph

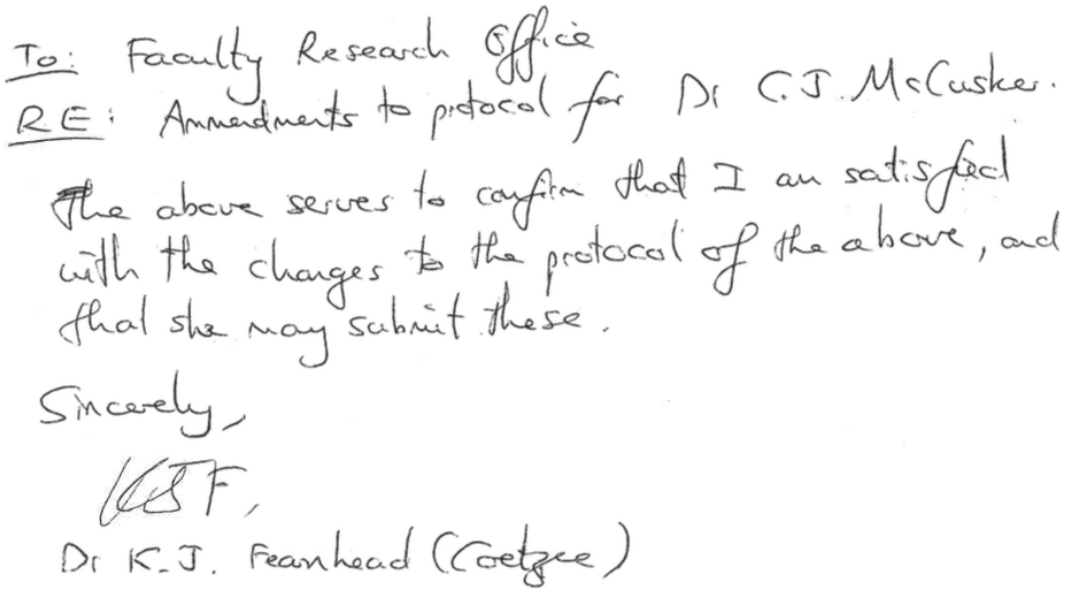
viii. h) Molecular characteristics

Page 6, 5th paragraph

I trust that these amendments are to your satisfaction and in keeping with the suggestions made by the assessors group.

Kind regards,

Casey McCusker



3.5 Appointment of supervisors

Postgraduate Office, Faculty of Health Sciences
Wits Medical School, 7 York Road, PARKTOWN, 2193, Johannesburg • Tel: (011) 717 2000 • Fax: (011) 717 2119

APPOINTMENT OF SUPERVISOR/S OF RESEARCH REPORT, DISSERTATION OR THESIS

Motivation / Reason for Appointment:

Both Drs Fearnhead and Rayne, a histopathologist and specialised breast surgeon respectively, have MMeds in their fields. They also both have a special interest and expertise in breast tumours. I have the utmost confidence that they will fulfil the role of Supervisor as expected by the Faculty.

Recommendation of Division / Department / School:

Dr Fearnhead: Division of Anatomical Pathology, School of Pathology, Faculty of Helath Sciences, Wits Medical School, University of the Witwatersrand

Dr Rayne : Department of Surgery, Faculty of Health Sciences, Wits Medical School, University of the Witwatersrand.

Student Surname and Initials: McCusker, C.J. Student Number: 1585560

Degree: MMed (Anat Path) Div / Dept / School: Division of Anatomical Pathology

Title: Adenomyoepithelioma of the breast: a case series.

Supervisor 1:	Dr Kirstin Janine Fearnhead (neé Coetzee)	
Supervisor Qualifications:	MBChB (UCT), FCPath SA(Anat), MMed (Anat Path)	
Supervisor Department:	Division of Anatomical Pathology	
Supervisor Telephone:	(011) 489 8491	E-mail: kirstin.coetzee@nhls.ac.za
Supervisor 2:	Dr Sarah Rayne	
Supervisor Qualifications:	BSc MBChB MRCS(Eng) MMed FCS(SA)	
Supervisor Department:	Department of Surgery	
Supervisor Telephone:	072 776 8553	E-mail: rayne.sarah@gmail.com

Student Signature: _____ **Supervisor 1** Signature: _____

Supervisor 2 Signature: _____

RECOMMENDATION BY HEAD OF ~~DIVISION~~ / DEPARTMENT / ~~SCHOOL~~:

HALE MJ (Surname and Initials) _____ (Signature) 14/9/2016 (Date)

APPROVAL BY ASSESSOR GROUP:

(On behalf of the FGSC) _____ (Signature) 14/9/2016 (Date)

FOR CIRCULATION TO THE FGSC

3.6 Addition of supervisor

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

14 August 2018
Person No: 1585560
SAC

Dr CJ McCusker
P.o Box 905-1072
Garsfontein
0042
South Africa

Dear Dr McCusker

Master of Medicine: Change of Supervisor

I would like to inform you that there has been a change in your supervision arrangements. *Kirstin Coetzee, Sarah Rayne, Pamela Michelow* will now be supervising you.

Please maintain regular contact with your Supervisor(s).

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

3.7 Turn-it-in similarity report

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Section 2: Draft article to Human Pathology, submission for original contribution:

2.1 Title page

Title:

Adenomyoepithelioma of the breast, a single-institution study of 17 cases.

Authors:

Dr. Casey Julia McCusker (MBChB)[a], Dr. Kirstin Janine Fearnhead (MBChB, FCPath (Anat), MMed)[a] and Prof. Sarah Louise Rayne (BSc, MBChB, MRCS, MMed, FCS)[b]

[a]Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand / National Health Laboratory Service, 7 York Road, Johannesburg, South Africa, 2193

[b]Helen Joseph Breast Care Clinic, Netcare Breast Care Centre, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 2193

Corresponding author at :

Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand / National Health Laboratory Service, 7 York Road, Johannesburg, South Africa, 2193. Phone number: +2782876451, email address: casey.mccusker@nhls.ac.za (CJ McCusker)

Keywords:

Breast; breast tumour; adenomyoepithelioma; adenomyoepithelial carcinoma; malignant adenomyoepithelioma; malignant AME.

Conflict of interest:

None.

Financial disclosure:

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Casey Julia McCusker (Student number: 1585560) am a student registered for the degree of MMed (Anat Path) in the academic year 2018.

I hereby declare the following:

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- I have followed the required conventions in referencing the thoughts and ideas of others.
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- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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1

Section 4 : Research Proposal

ADENOMYOEPITHELIOMA OF THE BREAST: A CASE SERIES.

Research Protocol

Dr Casey Julia McCusker

MBChB (UP)

Student number: 1585560

Degree registered for: MMed (Anat Path)

Registrar, Anatomical Pathology, Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service (NHLS), Johannesburg.

Supervisor:

Dr Kirstin Janine Fearnhead (neé Coetzee)

MBChB (UCT), FCPath SA(Anat), MMed (Anat Path)

Anatomical Pathologist, Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service (NHLS), Johannesburg.

Co-supervisors:

Prof Sarah Louise Rayne

BSc MBChB MRCS(Eng) MMed FCS(SA)

Specialist Surgeon, Helen Joseph Breast Care Clinic, Netcare Breast Care Centre. Lecturer, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

Dr Pamela Michelow

MBBCh MSc PGdip (HSE)

Cytopathologist, Division of Anatomical Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service (NHLS), Johannesburg.

4.1. Background and introduction

Adenomyoepithelioma (AME) is a rare, benign biphasic tumour comprising epithelial-lined spaces surrounded by a proliferation of myoepithelial cells [1]. It was first described in the breast by Hamperl in 1970 who suggested the term AME [2]. The World Health Organisation (WHO) 2012 classifies AME of the breast as a benign epithelial-myoepithelial lesion. Malignancy may arise in an AME and the WHO further subtypes AME with carcinoma (malignant adenomyoepithelioma) according to the location of the malignant component : luminal epithelium, myoepithelium or both (epithelial-myoepithelial carcinoma) [1].

In normal breast tissue and benign lesions, epithelial and myoepithelial components form the breast duct epithelium. Under neoplastic conditions, there is variation in the histologic appearance and immunophenotypic expression of myoepithelial cells, depending on whether the epithelial or myoid phenotype is expressed [2]. The combination of epithelial and myoepithelial cells can occur with considerable architectural and cytological heterogeneity within AME and poses diagnostic difficulty to the unwary, which may be compounded by the limited representation of lesional tissue on a needle core biopsy [3, 4]. Immunohistochemical investigation of the tumour, in order to correctly classify the lesion, is essential [4].

To the best of our knowledge, there are approximately 266 AME, 91 AME with carcinoma and 24 AME with other associated carcinoma, the majority as individual case reports and 7 cases series (Table. A.1) in the English language literature [3, 5-10].

A large number of AME with carcinoma were reviewed and reclassified according to the WHO 2012 classification by Xu et al [11].

AME affects mostly females and 2 rare cases are reported in male patients [4, 12, 13]. Patient age ranged between 22-92 years with a mean age of 59.1 years in the largest series [3]. The most common presentation of AME is a single, palpable, painless mass of variable duration [3, 4, 6, 14]. A single case of bilateral AME is reported [15].

Case series	Author	Year	Total number	Total number of AME	Recurrent	Malignant	Metastasis
1	Rosen et al [5]	1987	18	18	2	0	0
2	Decorsiere et al [6]	1988	U	17	U	U	U
3	Tavassoli [7]	1991	31	27	2	2	1
4	Loose et al [8]	1992	6	6	3	2	1
5	McClaren et al [3]	2005	35	23	0*	0	0
6	Hayes [9]	2011	25	12	2	13	4
7	Moritz [10]	2016	14	10	0	4	ND

Mammography of AME reveals a dense, round to lobulated, often circumscribed mass, resembling a fibroadenoma. Infrequently, ill-defined margins, calcifications and a cystic appearance are seen [4, 8, 14, 16-18]. Ultrasound reveals a round or oval, solid mass with a hypo- or complex echogenic texture and posterior or combined acoustic enhancement [9, 14, 19, 20]. Moritz et al, reported all AME in series of 14 cases as BI-RADS 4 or higher and the same series suggested that a definite diagnosis may not be possible radiographically.

AME ranges in size between 3mm to 70mm and AME with carcinoma may reach a much larger size, up to 170mm [4, 11]. AME may be round to lobulated, well circumscribed, firm or hard. Solid, cystic and nodular configurations have been described. At low-power, AME is circumscribed, comprises aggregated nodules without a discrete fibrous capsule and has a biphasic appearance due its dual epithelial-myoepithelial composition. High-power architecutre includes papillary,

pseudopapillary, trabecular and tubular and a combination of patterns can be seen [4, 6, 14, 21, 22]. Tavassoli subtyped AME into three variants, namely spindle-cell, tubular and lobular [6]. The cuboidal to columnar epithelial cells form round or ovoid glandular lumen invested by a proliferation of myoepithelial cells, which may assume a spindle, clear cell, plasmacytoid or epithelioid phenotype. Benign lesions may show a slightly increased mitotic activity, whereas malignant tumours show a marked increase, with rates varying between 10 and 40 mitoses per 10 high-power fields. Cytologic atypia with nuclear pleomorphism, prominent nucleoli, hyperchromasia and necrosis have been associated with tumours showing recurrence or may herald the development or presence of malignancy [6, 4, 11, 14]. Malignancy in an AME may arise either the epithelial, myoepithelial or both components [1, 8, 9].

Immunohistochemical staining of the epithelial cells with cytokeratin, epithelial lumen with EMA and staining of myoepithelial component with 2-3 of the following markers: p63, 34BE12, CK5/6, CK14, CD10 and actins (smooth muscle actin and muscle specific actin), highlights the tumour's biphasic nature. S100 may highlight both components [3, 4, 23]. Regarding the hormonal profile, oestrogen receptor and progesterone receptor may show weak, patchy positive staining and Her2-Neu is negative. The Ki-67 proliferation index is moderate and is commonly higher in the myoepithelial component [1, 4, 14]. Few studies evaluate the hormone receptor profile in AME and it is noted that salivary gland type tumours of the breast may express a triple negative phenotype, however exhibit low-grade behaviour [24].

Fine-needle aspiration of AME may be challenging and shows a cellular specimen comprising large clusters of epithelial and myoepithelial cells and single-lying cells with spindled and epithelioid morphology. Intranuclear cytoplasmic inclusions, foam cells and apocrine cells are infrequent findings [8, 14, 25-29]. AME with carcinoma shows hypercellular smears with loss of cohesion and a metachromatic matrix material, the latter is best appreciated on Diff-Quik stains [8, 25, 29, 30].

AME may be associated with squamous and sebaceous metaplasia [31, 32]. Concomitant AME and benign and malignant pathologies, namely collagenous spherulosis, phyllodes tumour, lobular neoplasia (atypical lobular neoplasia and invasive lobular carcinoma), ductal carcinoma in-situ (DCIS), invasive carcinoma of no special type, adenoid cystic carcinoma and low-grade adenosquamous carcinoma

are reported [8, 9, 33-46]. AME with carcinoma may rarely show heterologous osteogenic, spindle cell and carcinomatous differentiation [47].

Few studies have been undertaken to evaluate the molecular profile of AME [11]. Microsatellite instability for the D17S250 (17q11.2-BRCA1) microsatellite marker and loss of heterozygosity of the HPC1 gene have been reported [14]. Xu et al describe deletion of CDH1 and polysomy of CEP16 in myoepithelial cells by double fusion fluoresence in situ hybridisation (D-FISH). A report of a malignant AME with a lung metastasis shows a diploid DNA luminal epithelial population and tetraploid DNA myoepithelial cells. A point mutation of the p53 gene is reported, exclusively in the myoepithelial component [11].

Simple excision of most AME is curative and the recommended treatment of AME with carcinoma is wide local excision with adequate margins [6, 14]. Local recurrence has been reported and may be attributed to multinodular growth, intraductal extension of a lesion or incomplete excision [8]. Axillary lymph node metastasis of both AME and AME with carcinoma, in either or both components, has been described [6, 8, 48]. Distant metastasis of with AME with carcinoma is by haematogenous spread and sites include lung, liver, bone, thyroid, kidney, thoracic wall and brain [7, 16, 41, 44, 47, 49-57].

4.2. Aims

The aim of this study is to report a series of cases of AME of the breast, because this rare tumour may pose special considerations with respect to histological diagnosis and therapeutic management.

4.3. Objectives

1. To report a case series of AME of the breast.
2. To elucidate the clinical characteristic of this rare, benign tumour.
3. To describe the variability in the histology, including the immunohistochemical profile.
4. To document the co-occurrence of in-situ or invasive malignancy with these tumours.

4.4. Methods

4.4.1 Study Design

This will be a cross-sectional retrospective descriptive study.

4.4.2 Site of Study

The study will take place at the Division of Anatomical Pathology of the School of Pathology at the University of the Witwatersrand.

4.4.3 Time Period

All cases accessioned during the 18 year period from March 2000 to March 2018.

4.4.4 Study Sample

The study sample will be obtained from the Department of Anatomical Pathology at the Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals. Permission has been obtained from Professor MJ Hale to use the archives.

4.4.5 Inclusion and Exclusion Criteria

Inclusion criterion:

- Male and female patients, of any age, with a histological diagnosis of AME of the breast.

Exclusion criterion:

- Reported cases with a pathological diagnosis of AME with slides and/or paraffin embedded tissue blocks, which are not retrievable.

4.4.6 Methods

1. The cases reported during the study time frame will be identified by a computer-based record search. The cases are identifiable by a systematized nomenclature of medicine (SNOMED) code of 'myoepithelioma' and 'myoepithelial carcinoma' of the breast, entered into the NHLS database at the time of reporting of the specimens.
2. The reports of the cases identified will be obtained.
3. A second search using the patient's first name, surname, hospital number to correlate core biopsies and resection specimens will be performed.
4. The slides of the cases identified will be retrieved from the department's archival slide filing system.
5. The cases will be reviewed by both the principal investigator and the supervisor (Dr KJ Fearnhead).
6. The patient's clinical files will be reviewed, where possible.
7. The clinical and histologic parameters reviewed in the study will be recorded in the data sheet. See annexure A.

4.4.7 Statistical Analysis:

The study design aims to describe the clinico-pathological characteristics of a small group of rare, benign tumours of the breast that are presented in the form of a case series. The sample size is likely to be very small (<20 cases). The data will be expressed quantitatively as summary statistics and/or visually as graphs or tables.

The distribution of the data will be assessed and if, as anticipated, the distribution is not normal the median and interquartile ranges will be calculated. If on the other hand, the data distribution should be found to be normal, the range, mean and standard deviation will be calculated. Neither hypothesis testing nor use of inferential statistics is possible.

4.5. Funding

No funding will be needed.

4.6. Ethics

A project-specific application to the Human Research Ethics Committee (Medical) and Faculty of Health Sciences of the University of Witwatersrand, Postgraduate Office, will be submitted. There is blanket ethics approval (M150884) to use archived blocks, reports and slides in histological, IHC and molecular research.

The data sheet will be anonymous. Patient anonymity is paramount and to this end, the cases will be allocated a study number. A link will be created between the study number and the NHLS histology "case number", thus concealing the patient's identity. Patient confidentiality will be strictly maintained at all times. The patient's details will be kept anonymous and the patient's personal details will not be disclosed. This information will be kept in a locked cupboard in the registrar office at the Department of Anatomical Pathology, Medical School.

4.7. Time scale

	Jul '16	Aug '16	Sep '16	Oct '16	Nov '16	Dec '16	Jan '17	Feb '17	Mar '17	Apr '17
Presentation to department	12 Jul X									
Proposal to ethics			X							

Presentation to School of Pathology			14 Sep X							
Protocol submission		X								
Ethics approval				X						
Data retrieval/entry				X	X					
Data analysis						X	X			
Write-up								X	X	
Submission/ corrections										X

4.8. Task allocation

All data retrieval, assessment of histopathology reports, assessment and retrieval of clinical records and recording into data capture sheets, will be performed by the principle investigator, Dr CJ McCusker. The cases will be reviewed by both Dr McCusker and her supervisor, Dr Fearnhead.

4.9. Anticipated difficulties

Problems may be encountered in obtaining slides for the cases identified with AME as some of the 'older' cases may be irretrievable. If the slides are not available, the paraffin blocks may be retrieved and Haematoxylin and Eosin recuts obtained.

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