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**FIBROADENOMA COMPLEXO: REVISÃO BIBLIOMÉTRICA E
APRESENTAÇÃO DE CASO CLÍNICO**

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Trabalho de Conclusão de Curso apresentado
ao Curso de Medicina da FAHESP/IESVAP,
como requisito parcial para obtenção do Grau
de Bacharel em Medicina.

Orientador: Antonione Santos Bezerra Pinto

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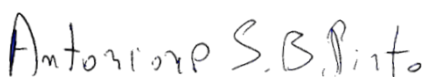
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Aprovado em 03 de dezembro de 2020.

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Dr. Elder Bontempo Teixeira

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RESUMO

Fibroadenomas (FAs) são tumores fibroepiteliais benignos da mama. Caracterizam-se como bifásicos, possuindo componentes estromais e epiteliais. Estima-se que afetem mais de 20% da população dos 16 aos 40 anos. FAs complexos são um subtipo que possuem uma ou mais características patológicas: calcificações epiteliais, metaplasias apócrinas, adenoma esclerosante e cistos maiores que 3mm. Segundo estudos, mulheres com FAs complexos tem 3,1 vezes maior risco de desenvolver câncer de mama. Objetivou-se mapear a produção científica internacional sobre Fibroadenoma Complexo. Foram usados os termos de busca: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”) em uma das principais bases de dados, a *ISI Web of Knowledge/Web of Science*TM, no recorte temporal entre os anos 1981 e 2019. Como percurso metodológico, foi realizada uma pesquisa bibliométrica em trabalhos acadêmicos na *Web of Science*TM, identificando-se, após aplicados os filtros de refinamento, 160 registros de publicação em 126 periódicos distintos. Ademais, realizou-se ainda a discussão de um caso clínico, através de revisão de prontuário e entrevista com a paciente.

Palavras-chave: Diagnóstico. Fibroadenoma. Tratamento.

ABSTRACT

Fibroadenomas (FAs) are benign fibro-epithelial tumours of the breast characterized by being biphasic and having stromal and epithelial components. It is estimated that FAs affect more than 20 percent of the general population aged 16-40 years old. Complex FAs are a sub-type of fibroadenoma presenting one or more pathological characteristics, such as epithelial calcifications, apocrine metaplasias, sclerosing adenoma and cysts larger than 3 mm. According to studies elsewhere, women with complex FAs are 3.1 times more likely to develop breast cancer. The objective of the present study was to map the scientific production of articles on complex FA in the international literature. The ISI Web of Knowledge (Web of Science), one of the main scientific databases in the world, was searched with the following terms: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”). Only articles published between 1981 and 2019 were considered for a bibliometric review, in which 160 articles from 126 different periodicals were identified after using refinement filters. Moreover, a clinical case was also discussed based on the patient’s medical record and interview.

Key-words: Diagnosis. Fibroadenoma. Treatment.

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FIBROADENOMA COMPLEXO: REVISÃO BIBLIOMÉTRICA E APRESENTAÇÃO DE CASO CLÍNICO

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RESUMO

Fibroadenomas (FAs) são tumores fibroepiteliais benignos da mama. Caracterizam-se como bifásicos, possuindo componentes estromais e epiteliais. Estima-se que afetem mais de 20% da população dos 16 aos 40 anos. FAs complexos são um subtipo que possuem uma ou mais características patológicas: calcificações epiteliais, metaplasias apócrinas, adenoma esclerosante e cistos maiores que 3mm. Segundo estudos, mulheres com FAs complexos tem 3,1 vezes maior risco de desenvolver câncer de mama. Objetivou-se mapear a produção científica internacional sobre Fibroadenoma Complexo. Foram usados os termos de busca: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”) em uma das principais bases de dados, a *ISI Web of Knowledge/Web of Science*TM, no recorte temporal entre os anos 1981 e 2019. Como percurso metodológico, foi realizada uma pesquisa bibliométrica em trabalhos acadêmicos na *Web of Science*TM, identificando-se, após aplicados os filtros de refinamento, 160 registros de publicação em 126 periódicos distintos. Ademais, realizou-se ainda a discussão de um caso clínico, através de revisão de prontuário e entrevista com a paciente.

Palavras-chave: Diagnóstico; Fibroadenoma; Tratamento.

1. INTRODUÇÃO

Fibroadenomas (FAs) são tumores fibroepiteliais benignos da mama¹, caracterizam-se como bifásicos, tendo em sua estrutura componentes estromais e epiteliais², que se desenvolvem na unidade lobular do ducto terminal³ e afetam principalmente meninas adolescentes e mulheres adultas jovens, tendo elevada incidência entre a segunda e a terceira década de vida⁴, no entanto podem ocorrer em qualquer idade².

Os FA são assintomáticos em cerca de 25% dos casos, múltiplos em 13-20% e bilaterais em 10-15%. São mais comuns na mama esquerda e sua localização predomina-se nos quadrantes superolaterais. Estima-se que afetem mais de 20% da população feminina dos 16 aos 40 anos, sendo esperado um valor real superior, devido muitas vezes serem nódulos assintomáticos⁵.

São estimulados por estrogênio, progesterona, gestação e lactação, e sofrem atrofia no período de menopausa⁶. Na maior parte dos casos se apresentam como massas mamárias que não ultrapassam 3-4cm. Além da sua forma habitual, o FA ainda pode apresentar-se, raramente, nas formas juvenil, gigante, extramamária e complexa⁷.

A patogênese do FA ainda não é clara. Entretanto, foi descoberta uma associação com a elevação da expressão do gene *B-cell lymphoma 2 (BCL-2)* nas células epiteliais dos FA. Além disso, também há uma relação com a mutação do gene *mediator complex subunit 12 (MED12)*, situado no cromossomo X, encontrada nas células do estroma⁵.

FAs complexos são um subtipo de FA que possuem uma ou mais características patológicas. Tanto FAs complexos quanto os simples frequentemente apresentam nódulos únicos e com orientação paralela à superfície da pele³.

No que diz respeito ao tamanho, quando comparados, percebe-se que FAs complexos são menores que FAs simples⁶. Isso ocorre em virtude de que os FAs tendem a regredir com a idade, perder sua celularidade e adquirir características histopatológicas complexas³.

Segundo estudo realizado, mulheres com FAs complexos tem 3,1 vezes maior risco relativo de desenvolver câncer de mama invasivo quando comparadas à população geral^{1,6}. O risco permanece elevado por pelo menos 20 anos após o diagnóstico¹, o que leva a necessidade de um acompanhamento longitudinal do paciente.

O tratamento da patologia pode variar de acordo com a idade da paciente e das dimensões do nódulo. Diante disso, o presente estudo visa à realização de uma revisão bibliométrica da literatura sobre FA complexo, além de apresentar um caso clínico com enfoque nas características imaginológicas e anatomopatológicas da doença.

2. MATERIAIS E MÉTODOS

O presente estudo trata-se de uma revisão bibliométrica e estudo de caso clínico. A primeira designa quantificar os processos de comunicação escrita através da área de estudo que utiliza a estatística e a matemática para oferecer uma base quantitativa ao remontamento de informações documentais⁸. Objetivou-se mapear a produção científica internacional sobre Fibroadenoma Complexo. Foram usados os termos de busca: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”) em uma das principais bases de dados, a *ISI Web of Knowledge/Web of Science*TM, no recorte temporal entre os anos 1981 e 2019, analisando os registros que apresentam os termos selecionados para a busca, com base em revisão de literatura sobre a temática em questão. Como percurso metodológico, foi realizada uma pesquisa bibliométrica em trabalhos acadêmicos na *Web of Science*TM, identificando-se, após aplicados os filtros de refinamento, 160 registros de publicação em 126 periódicos distintos. Foram considerados apenas artigos e revisões, excluindo-se todos materiais editoriais, capítulos de livros e artigos em eventos. Como principais resultados das análises foram identificados a quantidade de artigos em evolução, os *tops journals* da temática e os artigos mais citados.

O referido estudo também irá apresentar um relato de caso clínico de caráter descritivo, baseado na revisão do prontuário, entrevista com o paciente e registro dos métodos diagnósticos e tratamento utilizados. O paciente foi convidado a realizar a assinatura do Termo de Consentimento Livre e Esclarecido – TCLE em acordo as normas e diretrizes brasileiras que ordenam as pesquisas envolvendo seres humanos, incluindo as Resoluções nº 466/12 e 510/16 do Conselho Nacional de Saúde (CNS). O estudo foi submetido e aprovado no Comitê de Ética em Pesquisa (CEP) do Centro Universitário Tocantinense Presidente Antonio Carlos – UNITPAC (nº do parecer: 3.838.142).

3. RESULTADOS

Após realização do levantamento bibliométrico na principal coleção do *Web of Science*TM foram identificados 160 artigos sobre Fibroadenoma. Estes artigos estão publicados em 126 periódicos distintos indexados à base de dados em questão e foram escritos por 911 autores que possuem vínculos à 287 instituições, localizadas em 45 países. Para a consecução destes artigos foram utilizadas 4.157 referências, com uma média de aproximadamente 26 referências por artigo. Na Tabela 1, a seguir, são apresentados esses resultados.

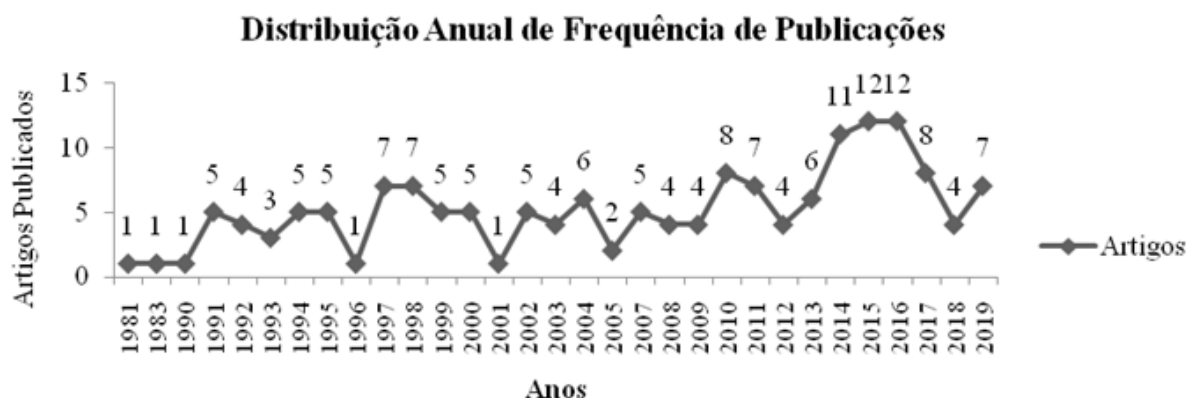
Tabela 1: Resultados Gerais do Levantamento Bibliométrico (1981-2019).

Dados Bibliométricos	Quantidade
Publicações (artigos)	160
Periódicos indexados	126
Autores	911
Instituições (vínculos dos autores)	287
Países	45
Referências citadas	4157

Fonte: Elaboração própria baseada nos resultados da pesquisa.

Apesar de a revisão bibliométrica ter sido realizada desde 1945-2019 (considerando-se apenas anos completos), o primeiro artigo só foi publicado em 1981, tendo um crescimento maior apenas a partir de 1991 (Figura 1 e Tabela 2). Considerando todos os anos em que ocorreu alguma publicação, obtêm-se a média de aproximadamente 5 publicações anuais.

Figura 1. Distribuição Annual de Frequência de Publicações (1981-2019).



Fonte: Elaboração própria baseada nos resultados da pesquisa.

Tabela 2: Distribuição anual das publicações (1981-2019).

Ano	Artigos	Citações	Ano	Artigos	Citações
1981	1	66	2004	6	186
1983	1	4	2005	2	81
1990	1	170	2007	5	723
1991	5	243	2008	4	69
1992	4	203	2009	4	125
1993	3	118	2010	8	157
1994	5	529	2011	7	115
1995	5	206	2012	4	28
1996	1	24	2013	6	41
1997	7	131	2014	11	221
1998	7	155	2015	12	179
1999	5	83	2016	12	171
2000	5	189	2017	8	17
2001	1	64	2018	4	2
2002	5	130	2019	7	9
2003	4	202			

Fonte: Elaboração própria baseada nos resultados da pesquisa.

A tabela abaixo (tabela 3), representa os periódicos com maior número de artigos publicados, destacando-se o Journal of Ultrasound in Medicine. Os demais periódicos, da 9ª à 21ª posição apresentaram dois artigos como resultado. O restante, a partir da 22ª posição apresentaram apenas 1 artigo publicado.

Tabela 3: Top periódicos com mais artigos publicados (1981-2018).

Periódicos	Quantidade de artigos	Citações	Citações/Quantidade
Journal of Ultrasound in Medicine	5	52	10,4
Breast Cancer Research and Treatment	4	71	17,5
Histopathology	4	145	36,5
International Journal of Cancer	4	220	55
American Journal of Surgical Pathology	3	135	45
Asian Pacific Journal of Cancer Prevention	3	22	7,33
Journal of Pathology	3	254	84,67
Pediatric Radiology	3	40	13,33

Fonte: Elaboração própria baseada nos resultados da pesquisa.

A tabela 4 demonstra a classificação dos autores com o maior número de publicações e o total de citações recebidas pelos mesmos. Os demais autores, da 8ª à 62ª posição apresentaram dois artigos como resultado. Os demais listados a partir da 63ª posição apresentaram um artigo.

Tabela 4: Autores com maior número de publicações (1980-2018).

Autores	Artigos	Citações	Afiliação (Instituição de vínculo)	País
Kim SJ	4	7	Myongji Hospital	Coréia do Sul
Reis JS	4	169	Memorial Sloan-Kettering Cancer Center	USA
Tan PH	4	194	Singapore General Hospital	Singapura
Brogi E	3	133	Memorial Sloan-Kettering Cancer Center	USA
Carney JA	3	135	Georgetown University	USA
de las Mulas JM	3	42	Universidade Nacional de Córdoba	Espanha
Millan Y	3	42	Universidade Nacional de Córdoba	Espanha

Fonte: Elaboração própria baseada nos resultados da pesquisa.

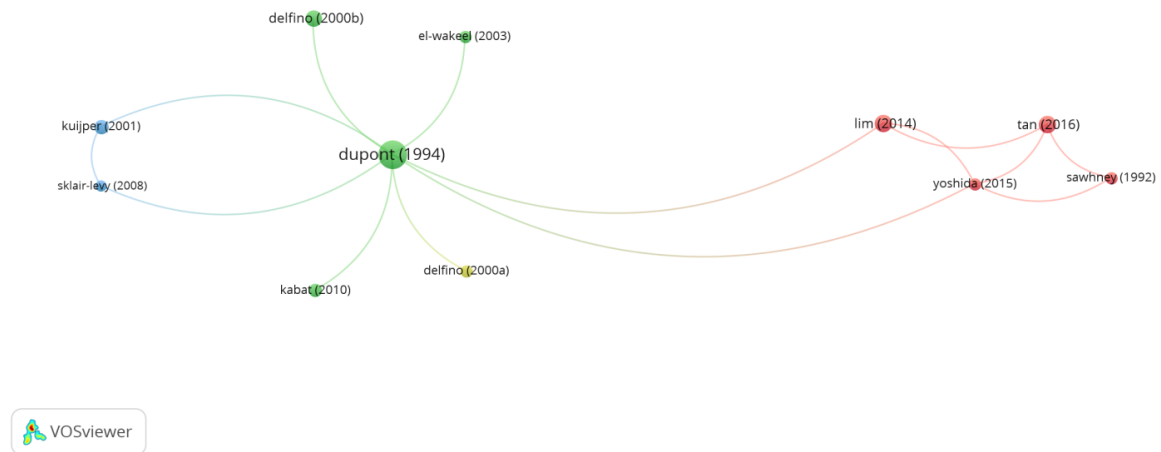
No que se refere ao número de artigos por país de acordo com as instituições de vínculo com os autores, os Estados Unidos da América lideram a lista das pesquisas, apresentando sozinho quase 30% do número total de publicações.

Tabela 5: Quantidade de artigos por país de origem das instituições de vínculo dos autores.

País	Quantidade	Citações
USA	47	2802
Itália	10	229
Reino Unido	10	647
França	8	147
Alemanha	7	57
Taiwan	7	60
Brasil	6	143
India	6	11
Japão	6	181
China	6	191

Fonte: Elaboração própria baseada nos resultados da pesquisa.

Dos 160 artigos analisados, 31 foram citados pelo menos 40 vezes, sendo selecionados para o gráfico abaixo sob os parâmetros do software VOSviewer. Destes, 11 apresentaram citações entre si e estão apresentados abaixo (Figura 2).

Figura 2. Artigos mais citados e mais relacionados entre si (1981-2019).

Fonte: Elaboração própria baseada nos resultados da pesquisa.

Em relação aos artigos mais citados, destacam-se Dupont *et al.*, Lim *et al* e Tan *et al.* (tabela 6).

Tabela 6: Artigos mais citados.

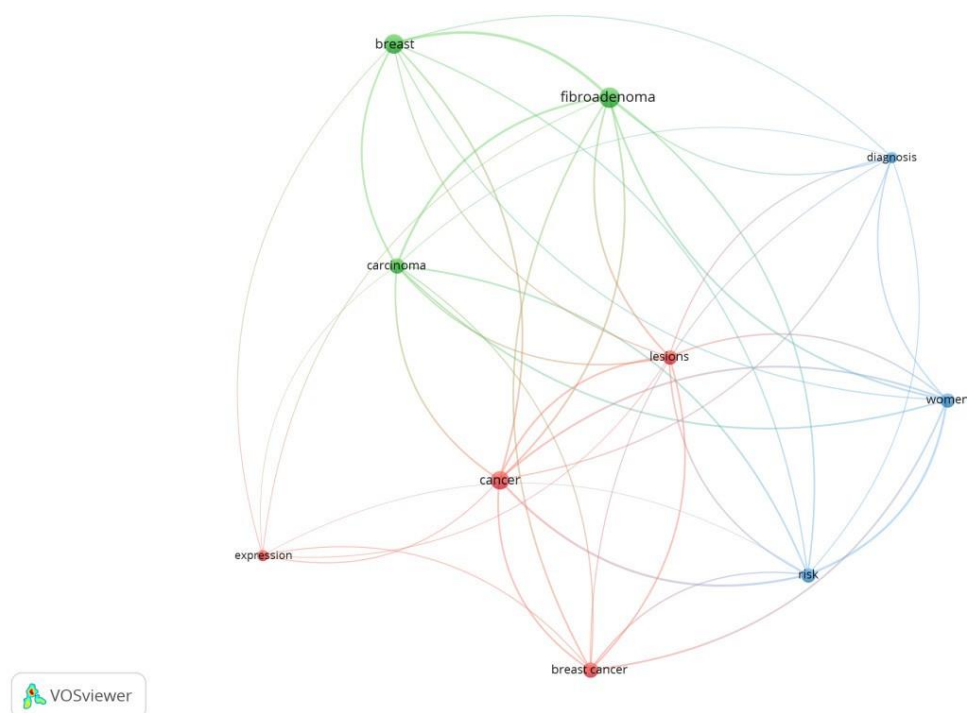
Autores/ano	Título	Fonte	Citações
Dupont et al. (1994)	Long-term risk of breast-cancer in women with fibroadenoma	New England Journal of Medicine	240
Delfino et al. (2000a)	Breast cancer, passive and active cigarette smoking and n-acetyltransferase 2 genotype	Pharmacogenetics	46
Delfino et al. (2000b)	Breast cancer, heterocyclic aromatic amines from meat and n-acetyltransferase 2 genotype	Carcinogenesis	80
Kuijper et al. (2001)	Histopathology of fibroadenoma of the breast	American Journal of Clinical Pathology	64
Sklair-Levy et al. (2008)	Incidence and management of complex fibroadenomas	American Journal of Roentgenology	43
El-Wakeel & Umpleby (2003)	Systematic review of fibroadenoma as a risk factor for breast cancer	Breast	44
Kabat et al. (2010)	A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer	Cancer Causes & Control	56
Lim et al. (2014)	Exome sequencing identifies highly recurrent med12 somatic mutations in breast fibroadenoma	Nature Genetics	91

Yoshida et al. (2015)	Frequent med12 mutations in phyllodes tumours of the breast	British Journal of Cancer	47
Tan et al. (2016)	Phyllodes tumours of the breast: a consensus review Epithelial stromal interactions in tumours – a	Histopathology	90
Sawhney et al. (1992)	morphologic study of fibroepithelial tumors of the breast	Cancer	

Fonte: Elaboração própria baseada nos resultados da pesquisa.

Entre as palavras-chave mais citadas nas publicações, estão fibroadenoma, carcinoma, cancer, expression e lesions (Figura 3).

Figura 3. Co-ocorrência de palavras mais citadas e mais relacionadas entre si (1981-2019).



Fonte: Elaboração própria baseada nos resultados da pesquisa.

4. RELATO DE CASO

Mulher, 26 anos, solteira e parda, procurou atendimento médico especializado em outubro de 2019 com história de nódulo em mama direita há 01 ano. Relatou crescimento recente, ausência de dor e sinais flogísticos. Na história clínica, negou doenças crônicas, tabagismo e etilismo; não fazia uso de nenhuma medicação contínua; menarca aos 11 anos,

nuligesta e sem história de câncer na família. Após exame físico completo, foi realizada a solicitação de exames complementares.

Realizou ultrassonografia mamária (USG) no dia 16/10/2019, que revelou a presença de dois nódulos em mama direita. O primeiro, ovalado, paralelo a pele, circunscrito, hipoecogênico, medindo 3,1 x 1,9 x 2,9cm, em junção dos quadrantes superiores, às 12h (Figura 4); e o segundo, ovalado, microlobulado, hipoecogênico, medindo 3,0 x 1,7 x 2,6cm, em quadrante ínfero-lateral, às 8h (Figura 5). Axilas com linfonodos de aspecto habitual. O laudo do exame trouxe a classificação *Breast Imaging Reporting and Data System* (BIRADS) 4, indicando lesão com alta suspeição de malignidade e sugerindo biópsia de nódulo às 8h.

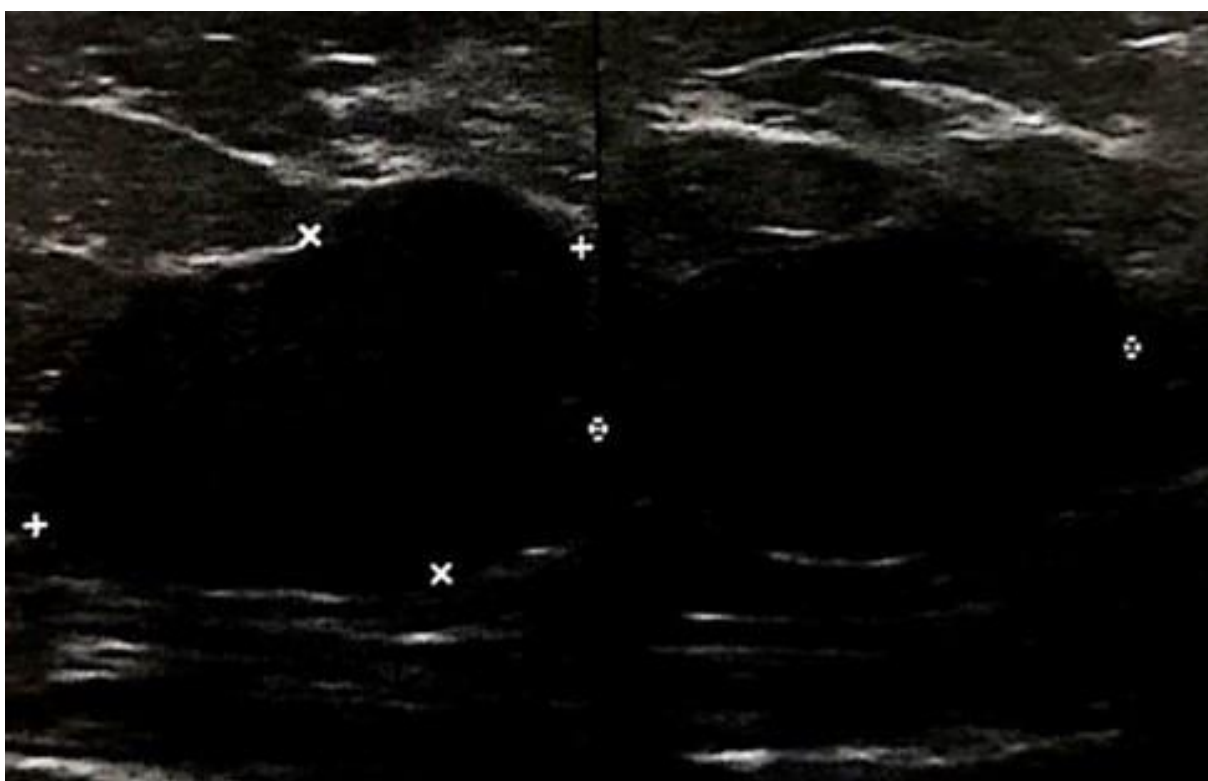


Figura 4: USG mama direita evidenciando nódulo ovalado, paralelo a pele, circunscrito, hipoecogênico, medindo 3,1 x 1,9 x 2,9cm, em junção dos quadrantes superiores.



Figura 5: USG mama direita evidenciando nódulo ovalado, microlobulado, hipocogênico, medindo 3,0 x 1,7 x 2,6cm em quadrante ínfero lateral.

Realizou Core Biopsy do nódulo microlobulado à direita no dia 22/10/2019. Os cortes histológicos revelaram mama com neoplasia benigna fibroepitelial, compatível com fibroadenoma complexo (Figura 6).

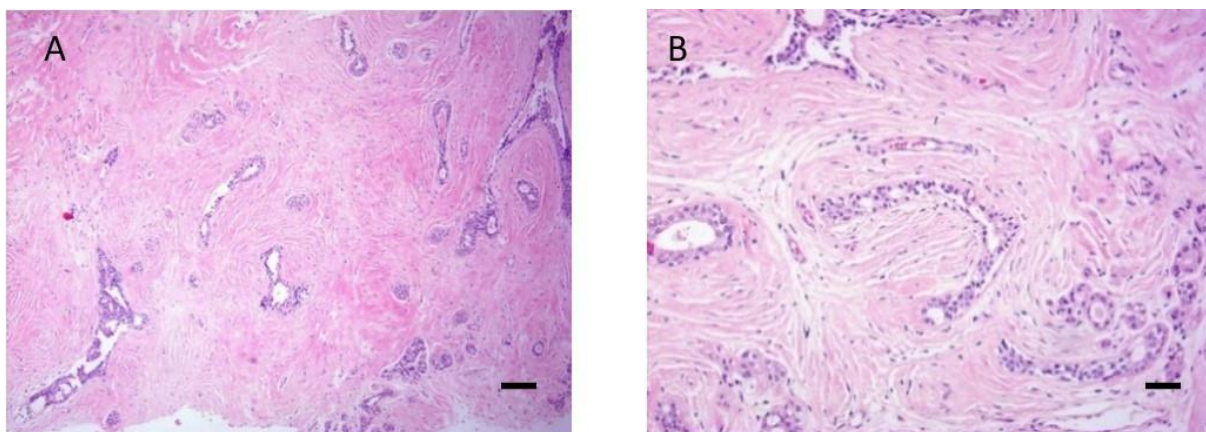


Figura 6 - A (aumento de 100x) e **B** (aumento de 400x): Foto microscopia em hematoxilina e eosina (H&E) revelam neoplasia benigna fibroepitelial caracterizada por proliferação ductal em padrão intra/pericanalicular e estroma colagenizado.

Após confirmação diagnóstica a paciente foi encaminhada ao cirurgião oncológico para avaliação. Este optou por realizar duas cirurgias em dias distintos, devido a não proximidade dos nódulos e a fim de evitar necrose de papila com a incisão areolar. Os procedimentos ocorreram nos dias 01/12/2019 e 21/01/2020. A biópsia foi repetida após a retirada dos nódulos, confirmando o diagnóstico de fibroadenoma complexo.

5. DISCUSSÃO

Após a revisão bibliométrica foi possível buscar documentos de alta qualidade científica indexados na Web of Science e ter uma visão geral da produção científica mundial, sendo observados apenas 160 artigos sobre fibroadenoma. Em relação à evolução anual da publicação, observa-se que primeiro artigo foi publicado em 1981, tendo um crescimento significativo apenas a partir de 1991, com média de 5 publicações anuais.

A maioria dos artigos são publicados em periódicos estrangeiros destacando-se o Journal of Ultrasound in Medicine com o maior número de artigos publicados. No que se refere ao número de artigos por país de acordo com as instituições de vínculo com os autores, os Estados Unidos Unidos da América lideram a lista das pesquisas, com quase 30% do número total de publicações. Quanto aos autores com artigos mais citados, destacam-se Dupont *et al.*, Lim *et al.* e Tan *et al.*

No caso descrito a paciente possui 26 anos, coincidindo com a faixa etária de maior incidência relatada na literatura. Entretanto, os FAs que foram encontrados estavam localizados na mama direita, um na junção dos quadrantes superiores às 12h, e o outro no quadrante inferior lateral às 8h, contradizendo com a localização habitual mencionada na literatura.

FAs complexos são um subtipo de FA que possuem uma ou mais características patológicas: calcificações epiteliais, metaplasias apócrinas, adenoma esclerosante e cistos maiores que 3mm. Entre suas características gerais mais frequentes pode-se citar a forma irregular, estrutura complexa de eco com componentes anecóicos e ecogênicos, além de contornos não circunscritos, que podem ser microlobulados, indistintos, espiculados e angulares. Algumas características literárias coincidem com as encontradas nos nódulos da paciente, como a microlobulação (nódulo à 8h) e orientação paralela à pele (nódulo à 12h), outras divergem, como o fato da paciente apresentar mais de um nódulo, se contrapondo à literatura.

No caso supracitado, o nódulo da paciente classificado como complexo por avaliação histopatológica, apresentava medidas menores que o FA simples (FA simples: 3,1 x 1,9 x 2,9cm; FA complexo: 3,0 x 1,7 x 2,6cm). O volume dos FAs pode aumentar 16% ao mês em mulheres com menos de 50 anos, já em mulheres que possuem 50 anos ou mais o volume aumenta 13% por mês, ou 20% em toda sua dimensão durante seis meses para mulheres de

todas as idades. Esse crescimento obrigatoriamente não indica um processo de malignidade, contudo caso o crescimento ultrapasse esses limites é recomendada uma excisão⁹.

Quanto a patogênese, há uma relação com o aumento da expressão do gene *BCL-2*, esse é responsável pela prevenção da apoptose⁵, permitindo manutenção do equilíbrio entre proliferação e morte celular programada, mecanismo pelo qual células com ácido desoxirribonucleico (DNA) danificado podem ser removidas sem prejuízo¹⁰.

Ademais, foi relatado que o *MED12* é um dos genes mais frequentemente mutados nos FAs e está localizado no cromossomo *Xq13.1*. A alta prevalência de mutações *MED12*, em tumores fibroepiteliais sugere que é um gene condutor somático da tumorigênese fibroepitelial. As mutações foram relatadas no exon 2 do gene *MED12*. Ele codifica para uma proteína que interage com proteína CDK8 (proteína quinase humana)/ CDK19, CYCC e *MED13*, formando um complexo mediador da RNA (ácido ribonucleico) polimerase II, que participa da regulação da transcrição, fazendo com que ele seja potencial no desenvolvimento de FA. Além disso, verificou-se que o códon 44 era altamente mutado e representa 86% das mutações observadas de FA¹¹.

O manejo de pacientes mais jovens geralmente é mais conservador quando critérios clínicos, histológicos, de imagem e de punção por agulha grossa sugerem lesão benigna. As lesões caracterizadas como BI-RADS 2 seguem a rotina de *screening*, já no BI-RADS 3 é necessário um acompanhamento sonográfico de seis meses, caso a lesão tenha sido observada na ultrassonografia, ou acompanhamento mamográfico se a lesão foi observada apenas na mamografia. FAs que não possuem achados atípicos podem ser monitorados por mamografia ou ultrassonografia duas vezes por ano durante dois anos e depois, anualmente⁶.

Na presença dos seguintes achados, é aconselhável a confirmação diagnóstica histológica por biópsia percutânea: achados ultrassonográficos inconclusivos (BI-RADS 4); evidência de tendência a crescer (clínica ou ultrassonográfica); nova massa palpável em paciente na menopausa; massa firme encontrada em uma paciente com fatores de risco em sua história, como história familiar positiva e/ou mutação *BRCA (breast cancer)*; massa com suspeita de microcalcificações na mamografia¹². Desse modo, quando a biópsia histopatológica releva uma lesão de risco elevado, é indicada biópsia excisional para descartar uma possível malignidade.

No referido caso, a paciente apresentava BI-RADS 4 a ultrassonografia. Na categoria 4, as lesões não possuem características morfológicas típicas de câncer, porém apresentam

real probabilidade de serem malignas, ocorrendo a sugestão de biópsia¹³. Através da análise do material colhido na biópsia, chegou-se ao diagnóstico de FA complexo.

A mamografia como método de diagnóstico primário para o FA oferece uma sensibilidade de 85%-95%, contudo sua especificidade é pequena, sendo assim fundamental a realização de outros métodos de diagnóstico¹³. No caso relatado, foi preferida a realização da ultrassonografia devido pacientes jovens apresentarem mamas de conteúdo denso, o que dificulta a visualização dos nódulos na mamografia.

Estudos demonstram que a sonoelastografia pode ser usada de forma complementar na avaliação mamária de massas indeterminadas, como o fibroadenoma, contribuindo para o acompanhamento e manejo clínico. Entretanto, também se faz necessário uma combinação da classificação de BI-RADS com a elastografia para um manejo mais eficiente¹⁵.

O tratamento da patologia pode variar de acordo com a idade da paciente e das dimensões do nódulo. Geralmente será feita um exérese simples quando o nódulo for maior que 2cm. Em nodulações menores e em pacientes com menos de 25 anos, é feito apenas acompanhamento clínico com segmento semestral, e a exérese só é indicada caso haja um crescimento rápido do FA e em mulheres acima de 35 anos⁷.

No caso, foi indicada a exérese dos nódulos devido a suas dimensões. Em virtude de pacientes diagnosticadas com FAs complexos possuir 3,1 vezes maior risco relativo de desenvolver câncer de mama invasivo e o risco permanecer elevado por pelo menos 20 anos após o diagnóstico^{1,6}, foi indicado um acompanhamento longitudinal do paciente, através de ultrassons semestrais.

6. CONSIDERAÇÕES FINAIS

Esta revisão bibliométrica possibilitou a discussão de 160 referências, que em algum momento abordaram o tema fibroadenoma complexo. A partir da caracterização e da análise das publicações supracitadas, ficam evidenciadas as muitas lacunas existentes na produção do conhecimento sobre a temática, visto que são poucos os artigos que se aprofundam na discussão do assunto específico.

Com a análise dos aspectos bibliométricos da produção científica, os profissionais da área da saúde e pesquisadores podem compreender as características dos artigos publicados.

Ademais, nota-se a extrema necessidade de maiores investigações e novos estudos, visto que na prática médica o FA complexo ainda é amplamente desconhecido entre clínicos gerais.

O estudo do caso clínico facilita o entendimento sobre maior compreensão acerca do FA complexo no seu mais variado contexto de características clínicas, exames de imagem e particularidades no estudo histopatológico, auxiliando o profissional de saúde na condução de tal diagnóstico.

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ANEXOS

ANEXO A - COMPROVANTE DE APROVAÇÃO NA REVISTA

De: Gil Facina <onbehalf@manuscriptcentral.com>
Enviado: quarta-feira, 30 de setembro de 2020 17:50
Para: polyanna_zimmermann@hotmail.com
<polyanna_zimmermann@hotmail.com>
Assunto: Mastology - Decision on Manuscript ID Mast-2020-0052.R2

30-Sep-2020

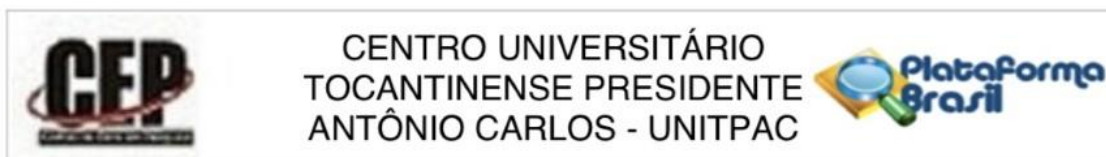
Dear Mrs. Zimmermann:

It is a pleasure to accept your manuscript entitled "Complex Fibroadenoma: Bibliometric Literature Review and Presentation of a Clinical Case" in its current form for publication in the Mastology.

Thank you for your fine contribution. On behalf of the Editors of the Mastology, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. Gil Facina
Editor-in-Chief, Mastology
facina@unifesp.br

ANEXO B - COMPROVANTE DE ACEITE AO CEP



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: FIBROADENOMA COMPLEXO: REVISÃO BIBLIOMÉTRICA, SISTEMÁTICA E APRESENTAÇÃO DE CASO CLÍNICO

Pesquisador: Antonione Santos Bezerra Pinto

Área Temática:

Versão: 1

CAAE: 27614719.5.0000.0014

Instituição Proponente: INSTITUTO DE EDUCACAO SUPERIOR DO VALE DO PARNAIBA LTDA.

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.838.142

Apresentação do Projeto:

FIBROADENOMA COMPLEXO: REVISÃO BIBLIOMÉTRICA, SISTEMÁTICA E APRESENTAÇÃO DE CASO

Objetivo da Pesquisa:

Realizar revisão bibliométrica e sistemática, além de um estudo de caso clínico de um paciente diagnosticado com FA complexo e pautar os principais aspectos da doença, incluindo tratamento e características histopatológicas e de imagem, para confrontá-los a partir da utilização de estudos pré-existentes.

Avaliação dos Riscos e Benefícios:

Avaliação adequada. Os autores descrevem possíveis problemas e desconfortos produzidos pela participação e exposição do caso descrito pela pesquisa proposta. Declaram os cuidados em minimizar tais problemas, assim como, relatam os benefícios ao participante da pesquisa.

Comentários e Considerações sobre a Pesquisa:

Pesquisa exequível, e relevante para a área de estudo.

Endereço: Av. Filadélfia, nº 568, Setor Oeste.

Bairro: Araguaína

UF: TO

Município: ARAGUAINA

Telefone: (63)3411-8500

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E-mail: cep@unitpac.edu.br



**CENTRO UNIVERSITÁRIO
TOCANTINENSE PRESIDENTE
ANTÔNIO CARLOS - UNITPAC**



Continuação do Parecer: 3.838.142

Considerações sobre os Termos de apresentação obrigatória:

Apresentação de termos em acordo com a resolução CNS 466/12.

Recomendações:

Nenhuma

Conclusões ou Pendências e Lista de Inadequações:

Recomendo a aprovação do protocolo de pesquisa apresentado.

Considerações Finais a critério do CEP:

Colegiado vota com relator

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1488685.pdf	29/12/2019 10:04:50		Aceito
Orçamento	orcamento.docx	29/12/2019 10:04:16	Antonione Santos Bezerra Pinto	Aceito
Cronograma	cronograma.docx	29/12/2019 10:02:52	Antonione Santos Bezerra Pinto	Aceito
Outros	declaracaosobredestinacaodosdados.jpg	26/12/2019 17:39:45	Antonione Santos Bezerra Pinto	Aceito
Outros	divulgacaodosresultados.jpg	26/12/2019 17:33:10	Antonione Santos Bezerra Pinto	Aceito
Outros	cartaencaminham.jpg	26/12/2019 17:28:44	Antonione Santos Bezerra Pinto	Aceito
Declaração de Instituição e Infraestrutura	termodeanufibro.jpg	26/12/2019 17:26:26	Antonione Santos Bezerra Pinto	Aceito
Projeto Detalhado / Brochura Investigador	projetoCompleto.docx	26/12/2019 17:25:55	Antonione Santos Bezerra Pinto	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	tclefibroadenoma.doc	26/12/2019 17:19:30	Antonione Santos Bezerra Pinto	Aceito
Folha de Rosto	folhaderostofirbroaden.pdf	26/12/2019 11:06:57	Antonione Santos Bezerra Pinto	Aceito

Situação do Parecer:

Aprovado

Endereço: Av. Filadélfia, nº 568, Setor Oeste.

Bairro: Araguaína

UF: TO

Município: ARAGUAINA

Telefone: (63)3411-8500

CEP: 77.816-540

E-mail: cep@unitpac.edu.br

ANEXO C - NORMAS DE SUBMISSÃO DA REVISTA

Introduction

Mastology is an international, multidisciplinary Journal, and official publication of the Brazilian Society of Mastology. It focuses on translational and clinical research of breast diseases. All manuscripts will be initially accessed by the Editor for suitability for the Journal. Papers deemed suitable are then evaluated by at least two independent expert reviewers, in a blindreview process to assess the scientific quality of the paper. The Editor is responsible by the final decision regarding acceptance or rejection of articles. Those that do not have merit, which contain significant methodological errors, or that do not fit into the editorial policy of the Journal will be rejected and can not be appealed. The reviewers' comments will be returned to the Authors for modifications in the text or justification of their conservation. Only after final approval of the reviewers and Editors, will the manuscripts be forwarded for publication. All manuscripts accepted for publication shall become the property of the Journal and may not be edited, in whole or in part, by any other means of dissemination, without the prior written authorization issued by the Editor-in-Chief.

Ethics

If the paper involves the use of human subjects, the Authors should ensure that it has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The Journal will not accept editorial material for commercial purposes.

Submission of manuscripts

Articles can be sent in Portuguese, Spanish or English. After approved, all papers will be translated to English. Mastology publishes the following categories: Editorials, Original Articles, Short Communications, Review Articles, Images in Mastology, Case Reports, Technical Innovations, and Letters to the Editor. Original Articles: Describes experimental research or clinical research – prospective or retrospective, randomized or double blind. They must have 3,000 to 5,000 words, excluding illustrations (tables, figures [maximum of 5]) and references [maximum of 30]. Manuscripts containing original clinical or experimental research results will be prioritized for publication. All manuscripts must present: Title in English, Structured Abstract, Keywords, Abstract, Keywords, Introduction, Methods, Results, Discussion, Conclusions and References.

Short Communications: Reports on important new results that fall within the scope of the journal may be submitted as short communications. These papers should not exceed 2,000 words in length and 20 references, and should follow the structure of an original research paper.

Review Articles: Systematic critical evaluation of the literature on a given subject, so as to contain a comparative analysis of the works in the area, which discusses the limits and methodological scope, allowing to indicate perspectives of continuity of studies in that line of research and should contain conclusions. The procedures adopted for the review, as well as

the search, selection and evaluation strategies of the articles should be described, clarifying the delimitation and limits of the theme. Its maximum length should be 5,000 words and the maximum number of bibliographical references of 60.

The selection of themes is based on planning established by the Editor-in-Chief and CoEditors. Articles in this category are usually ordered by publishers from authors with proven experience in the field. Spontaneous contributions may be accepted. It must present: Title, Abstract (without need of structuring), Keywords, Text (with or without subtitles), and References. The general instructions for figures, tables and references are the same as for the original articles.

Images in Mastology: Unusual images in clinical practice or associated with topics which are considered as rare. The text will be continuous, expressing the rarity or singularity of the case, at maximum of 400 words, and no more than 10 references and 3 figures. They must present: Title, Abstract (non-structured up to 150 words), Keywords, and References.

Case reports: They are manuscripts reporting unpublished, highly interesting and well-documented clinical cases from a clinical and laboratorial point of view. The text should express the rarity or singularity of the case, at maximum of 2,000 words, and no more than 20 references and 3 figures. They should observe the structure: Introduction, Case report (with patient description, results of clinical exams, follow-up, diagnosis), Discussion (with similarity data in the literature), and Conclusion. They must present: Abstract (unstructured), Keywords, and up to 20 References.

Letters to the Editor: They aim to comment or discuss papers published in the journal or report original research in progress. They will be published at the discretion of the Editors, with the corresponding reply where applicable. They must not exceed 600 words and 5 references.

Editorials: Editorials are commissioned by the Editors, commenting on relevant works of the Journal itself, relevant researches or communications from Editors. Authors who wish to contribute an Editorial to the Journal should contact the Editorial Office (biblioteca@sbmastologia.com.br) prior to writing and submitting the Editorial.

Preparation of the Manuscript

A) Cover sheet

- Title of the article, in Portuguese and English, containing between 10 and 12 words, without Articles and prepositions. The Title should be motivating and should give an idea of the objectives and content Of work;
- full name of each author, without abbreviations;
- indication of the academic degree and institutional affiliation of each author, separately. If there is more than one institutional affiliation, indicate only the most relevant;
- indication of the Institution where the work was done;
- name, address, fax and e-mail of the corresponding author;
- sources of research assistance, if any;
- declaration of non-existence of conflicts of interest.

B) Second sheet

Abstract and Descriptors: Abstract, in Portuguese and English, with a maximum of 250 words.

For the original articles, should be structured (Objective, Methods, Results, Conclusions), highlighting the most significant data of the work. For case reports, revisions or updates and a previous note, the summary should not be structured. Below the abstract, specify at least five and at most ten descriptors (Keywords) that define the

subject of the work. The descriptors should be based on the DECS – Descriptors in Health Sciences – available at <http://www.decs.bvs.br>

C) Text

You should strictly obey the structure for each category of manuscript. In all manuscript categories, the citation of the authors in the text should be numeric and sequential.

Using Arabic numerals in parentheses and envelopes.

The standards to be followed were based on the format proposed by the International Committee of Medical Journal Editors and published in the article Uniform requirements for manuscripts submitted to biomedical journals also available for consultation at <http://www.icmje.org/>.

Presentation of the text

Preferably use the Microsoft Word® word processor.

Do not emphasize excerpts from the text: do not underline and do not use bold.

Do not use capital letters in proper nouns (other than the first letter) in the text or Bibliographical References. When using acronyms or abbreviations, describe them in full the first time they are mentioned in the text.

Summary

The Summary should contain the relevant information, allowing the reader to get a general idea of the work. All articles submitted must have a summary in Portuguese or Spanish and in English (abstract), between 150 and 250 words. For Original Articles, abstracts should be structured including objectives, methods, results and conclusions. For the other categories, the format of the abstracts may be the narrative, but preferably with the same information.

They should not contain quotations and abbreviations. Highlighting at least three and at most six indexing terms, extracted from the vocabulary “Descriptors in Health Sciences” (DeCS – www.bireme.br), when accompanying the abstracts in Portuguese or Spanish, and Medical Subject Heading – MeSH ([Http://www.nlm.nih.gov/mesh/](http://www.nlm.nih.gov/mesh/)), when they follow the “Abstract”. If no descriptors are available to cover the subject of the manuscript, terms or expressions of known use may be indicated.

Introduction

In this section, show the current state of knowledge about the topic under study, divergences and gaps that may possibly justify the development of the work, but without extensive review of the literature. For Case Reports, present a summary of the cases already published, epidemiology of the reported condition and a justification for the presentation as an isolated case. Clearly state the objectives of the work.

Methods

Start this section indicating the work planning: whether prospective or retrospective; Clinical or experimental trial; Whether the distribution of cases was random or not, and so on. Describe the criteria for selection of patients or experimental group, including controls. Identify the equipment and reagents used. If the applied methodology has already been used, give the references in addition to the brief description of the method. Also describe the statistical methods employed and the comparisons for which each test was used. In the Case Reports, the sections Material and Methods and Results are replaced by the description of the case, remaining the remaining cases.

Results

It should be limited to describing the results found without including interpretations and comparisons. Present the results in logical sequence, with text, tables and figures.

Discussion

It should properly and objectively explore the results, discussed in light of other observations already recorded in the literature, highlighting the new and original information obtained in the research. Emphasize the appropriateness of the research methods used. Compare and relate the observations with those of other authors, commenting and explaining the differences that occur. Explain the implications of the findings, their limitations, and make recommendations. The discussion should culminate with the conclusions, indicating ways for new research or implications for professional practice. For Case Reports, base the Discussion on a broad and updated literature review.

Thanks

Collaborations of individuals, institutions or acknowledgments for financial support, technical aids, deserving recognition, but not justifying inclusion as the author, should be included.

References

References should be listed at the end of the article, numbered consecutively, following the order in which they were first mentioned in the text, based on the Vancouver style (see: “Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Medical Publication” [http://www.nlm.nih.gov/bsd/uni-form_requirements.html]). All authors and works cited in the text should be included in this section and vice versa.

Articles accepted for publication may be cited accompanied by the expression: accepted and awaiting publication, or “in press” indicating the periodical, volume and year. For all references, cite all authors up to six. When in greater numbers, cite the first six authors followed by the expression et al. Examples:

Articles of Journals or Magazines

Del Giglio A, Pinhal MA. Genetic profile in breast cancer: a brief review for the mastologist. *Rev Bras Mastologia*. 2005; 15 (1): 45-50.

My Account

Montoro AF. *Mastology*. São Paulo: Sarvier, 1984.

Book Chapters

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. *Williams Obstetrics*. 22nd ed. New York: McGraw-Hill; 2005. Chapter 39, Multifetal gestation. P. 911-43.

With authorship

Von Hoff DD, Hanauske AR. Preclinical and early clinical development of new anticancer agents. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, et al. Editors. *Holland-Frei cancer medicine*. 7th ed. Hamilton (ON): BC Decker Inc .; 2006. p. 600- 16.

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Steinmacher DI. Evaluation of percutaneous needle biopsy with automatic propellant in the propaedeutics of palpable and nonpalpable lesions of the breast [dissertation]. São Paulo: Federal University of São Paulo. Paulista School of Medicine; 2005.

Electronic publications

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Tables and Figures

The presentation of this material should be in black and white, on separate sheets, with captions and respective numbers printed next to each illustration. The name of the manuscript and authors must be noted on the back of each figure and table. All tables and figures should also be sent in digital files, preferably in Microsoft Word ® files and the rest in Microsoft Excel ®, Tiff or JPG files. The quantities, units and symbols used in the tables must comply with the national nomenclature. Surgery and biopsy photographs where colorations and special techniques were used will be considered for color printing and the authors will be responsible for the additional cost. Captions: Print the captions using double space, accompanying the respective figures (graphics, photographs and illustrations) and tables. Each caption should be numbered in Arabic numerals, corresponding to its citations in the text. Abbreviations and Acronyms They must be preceded by the full name when first mentioned in the text. In tables, figures should be to contain their meaning below the table. If the illustrations have already been published, they must be accompanied by written authorization from the author or publisher, with the reference source where it was published. The text entered in the program “Word for Windows, with double space, with letters of size that makes reading easier (we recommend those of No. 14). It must be submitted electronically through the address: biblioteca@sbmastologia.com.br The Mastology reserves the right not to accept for evaluation the articles that do not fulfill the criteria formulated above. Submission of the manuscript The manuscript must be accompanied by a letter signed by all the authors, authorizing its publication, stating that it is unpublished and that it was not, or is being submitted for publication in another periodical. All persons designated as authors must respond for the authorship of the manuscript and have participated sufficiently in the work to assume public responsibility for its content. Authorship credit should be based only on substantial contributions during: (1) designing, planning, executing, analyzing and interpreting the results, (2) writing or reviewing the manuscript in an intellectually important way, and (3) Be published. Editors may request justification for inclusion of authors during the review process, especially if the total number of authors exceeds six.

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ANEXO D – VERSÃO EM INGLÊS

Complex Fibroadenoma: Bibliometric Literature Review and Presentation of a Clinical Case

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ABSTRACT

Fibroadenomas (FAs) are benign fibro-epithelial tumours of the breast characterized by being biphasic and having stromal and epithelial components. It is estimated that FAs affect more than 20 percent of the general population aged 16-40 years old. Complex FAs are a sub-type of fibroadenoma presenting one or more pathological characteristics, such as epithelial calcifications, apocrine metaplasias, sclerosing adenoma and cysts larger than 3 mm. According to studies elsewhere, women with complex FAs are 3.1 times more likely to develop breast cancer. The objective of the present study was to map the scientific production of articles on complex FA in the international literature. The ISI Web of Knowledge (Web of Science), one of the main scientific databases in the world, was searched with the following terms: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”). Only articles published between 1981 and 2019 were considered for a bibliometric review, in which 160 articles from 126 different periodicals were identified after using refinement filters. Moreover, a clinical case was also discussed based on the patient’s medical record and interview.

Key-words: Diagnosis; Fibroadenoma; Treatment.

1. INTRODUCTION

Fibroadenomas (FAs) are benign fibro-epithelial tumours of the breast¹, characterised by being biphasic and having stromal and epithelial components². They develop in the lobular unit of the terminal duct³ and affect mainly adolescent girls and adult young women. FAs occur with high incidence in the second and third decades of life⁴, although they may also occur at any age².

FAs are asymptomatic in about 25% of cases, multiple in 13-15% and bilateral in 10-15% of them cases, being more common in the left breast and predominantly located in the superior-lateral quadrants. Estimates believe that more than 20% of the female population aged 16-40 years old is affected, but a higher number should be expected seen that the nodules are often asymptomatic⁵.

FAs are stimulated by estrogen, progesterone, gestation and lactation, and become atrophied in the menopause period⁶. In most cases, they present as mammary masses not greater than 3-4 cm. In addition to its usual form of presentation, FAs may uncommonly occur in the juvenile, giant, extra-mammary and complex forms⁷.

The pathogenesis of FA is still not clear. However, an association with high expression of the B-cell lymphoma gene (BCL-2) in epithelial cells of FA was discovered. In addition, there is also a relation with the mutation in the mediator complex subunit 12 gene (MED12), located on the chromosome X in stroma cells⁵.

Complex FAs are a sub-type of fibroadenoma having one or more pathological characteristics. Both complex and simple FAs frequently show single nodules in parallel to the skin surface³.

As to size, complex FAs are smaller than simple ones⁶. This occurs because FAs tend to recede with age, lose cellularity and acquire complex histopathological features³.

According to a study, women with complex FAs are 3.1 times more likely to develop invasive breast cancer compared to general population^{1,6}. This risk remains high for at least 20 years after diagnosis¹, which leads to the need of following up the patient longitudinally.

Treating of FAs can range depending on the patient's age and nodule's size. In view of this, the present study is aimed at conducting a bibliometric review of the literature on

complex FA, in addition to showing a clinical case based on imaging and anatomopathological characteristics of the disease.

2. MATERIALS & METHODS

The present study is a bibliometric review aimed at quantifying the written communication process by using statistics and mathematics so that a quantitative basis can be provided to date back to documentary information⁸. In addition, the scientific production on complex FA in the international literature was also mapped. The ISI Web of Knowledge (Web of Science), one of the main scientific databases in the world, was searched with the following terms: (“complex” and “fibroadenoma”) or (“fibroadenoma” and “complex”). Only articles published between 1981 and 2019 were included for a bibliometric literature review on the theme. The methodology used refinement filters to identify related articles on the ISI Web of Knowledge database, in which 160 ones were from 126 different journals. Only articles and reviews were included, whereas editorials, book chapters, and event publications were excluded. The main results of this analysis were the quantity of studies in progress, the top journals on the theme, and the most cited articles.

The present study also described a clinical case report based on the patient’s medical record and interview, including diagnostic methods and treatments used. The patient was asked to sign an informed consent form, according to the Brazilian norms and regulations on human research, including Resolutions No. 466/12 and 510/16 of the National Health Council (CNS). This study was approved by the Research Ethics Committee of the Instituto Tocantinense Presidente Antonio Carlos (UNITPAC), according to Protocol No. 3838142.

3. RESULTS

After the bibliographic review on the ISI Web of Knowledge (Web of Science) database, a total of 160 articles on fibroadenoma was identified. These articles were published in 126 different journals indexed on this database and written by 911 authors, linked to 287 institutions located in 45 countries. All these articles used 4,157 references, approximately 26 each, on average. Table 1 lists the results below.

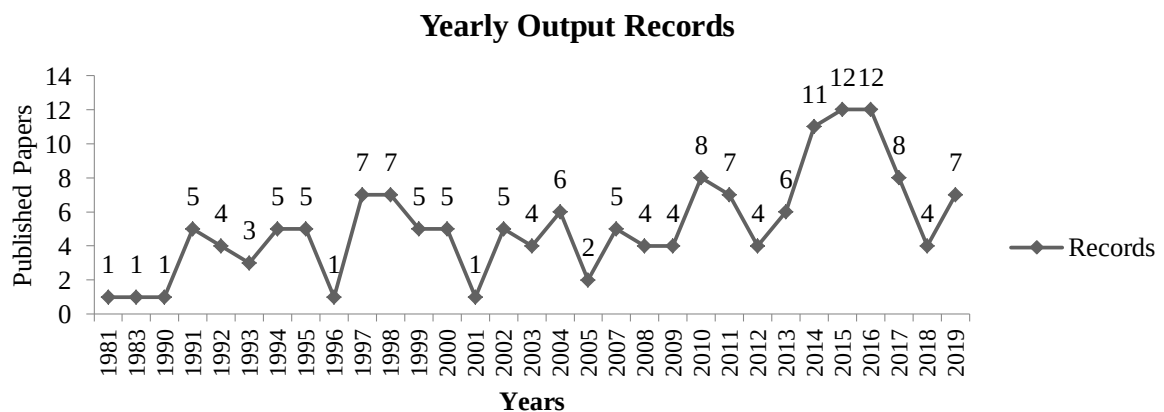
Table 1 - General results of bibliometric review (1981-2019).

Bibliometric data	Quantity
Publications (articles)	160
Indexed journals	126
Authors	911
Institutions (links of authors)	287
Countries	45
Cited references	4,157

Source: Own elaboration based on research results.

Although this bibliographic review has been performed for the 1945-2019 period (full years only), the first article was only published in 1981 and publications on the theme increased from 1991 onwards (Figure 1 and Table 2). Considering all the years in which there was a publication, approximately five articles were published per year, on average.

Figure 2. Yearly records of published articles (1981-2019).



Source: Own elaboration based on research results.

Table 2. Yearly records of published articles (1981-2019).

Years	Articles	Citations	Year	Articles	Citations
1981	1	66	2004	6	186
1983	1	4	2005	2	81
1990	1	170	2007	5	723
1991	5	243	2008	4	69
1992	4	203	2009	4	125
1993	3	118	2010	8	157
1994	5	529	2011	7	115

1995	5	206	2012	4	28
1996	1	24	2013	6	41
1997	7	131	2014	11	221
1998	7	155	2015	12	179
1999	5	83	2016	12	171
2000	5	189	2017	8	17
2001	1	64	2018	4	2
2002	5	130	2019	7	9
2003	4	202			

Source: Own elaboration based on results of the research.

Table 3 (below) shows the journals with the highest quantity of published articles, highlighting the Journal of Ultrasound in Medicine. The other journals that ranked from 9th to 21st had two articles; and those that ranked from 22nd onwards had only one article.

Table 3 - Top journals with the most articles published (1981-2018).

Journals	Number of articles	Citations	Citations/Quantity
Journal of Ultrasound in Medicine	5	52	10.4
Breast Cancer Research and Treatment	4	71	17.75
Histopathology	4	145	36.25
International Journal of Cancer	4	220	55
American Journal of Surgical Pathology	3	135	45
Asian Pacific Journal of Cancer Prevention	3	22	7.33
Journal of Pathology	3	254	84.67
Pediatric Radiology	3	40	13.33

Source: Own elaboration based on research results.

Table 4 shows the ranking of authors with the highest number of published articles and their total citations. The other authors that ranked from 8th to 62nd had two articles published, whereas those that ranked from 63rd onwards had only one.

Table 4 - Authors with the most articles published (1980-2018).

Authors	Articles	Citations	Affiliation (link institutions)	Country
Kim SJ	4	7	Myongji Hospital	South Korea
Reis JS	4	169	Memorial Sloan-Kettering Cancer Center	USA
Tan PH	4	194	Singapore General Hospital	Singapore

Brogi E	3	133	Memorial Sloan-Kettering Cancer Center	USA
Carney JÁ	3	135	Georgetown University	USA
de las Mulas JM	3	42	National University of Cordoba	Spain
Millan Y	3	42	National University of Cordoba	Spain

Source: Own elaboration based on research results.

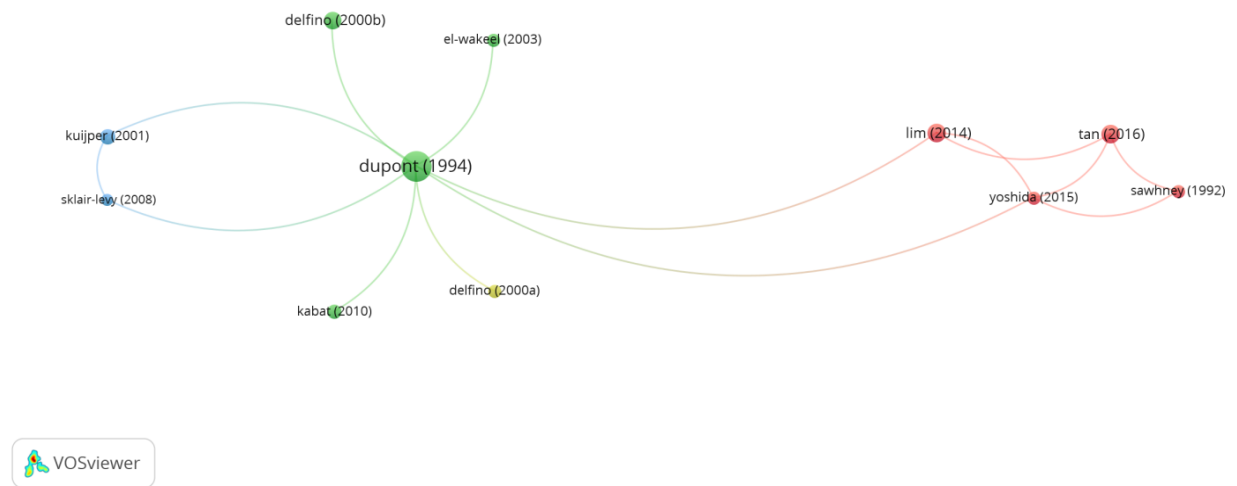
As to the number of articles published per country and according to each author's institution, the United States leads the list of research as they account for 30% of the total number of publications.

Table 5. Number of articles by country of origin of the authors' link institutions.

Country	Amount	Citations
USA	47	2.802
Italy	10	229
United Kingdom	10	647
France	8	147
Germany	7	57
Taiwan	7	60
Brazil	6	143
India	6	11
Japan	6	181
China	6	191

Source: Own elaboration based on research results.

Of the 160 articles reviewed, 31 were cited at least 40 times and selected according to the parameters of the software VOSviewer. Of these, 11 articles had citations between each other and are shown in figure 2.

Figure 2. Most cited and most related articles (1981-2019).

Source: Own elaboration based on research results.

As to the most cited articles, Dupont *et al.*, Lim *et al.* and Tan *et al.* (Table 6) are highlight.

Table 6. Most cited articles.

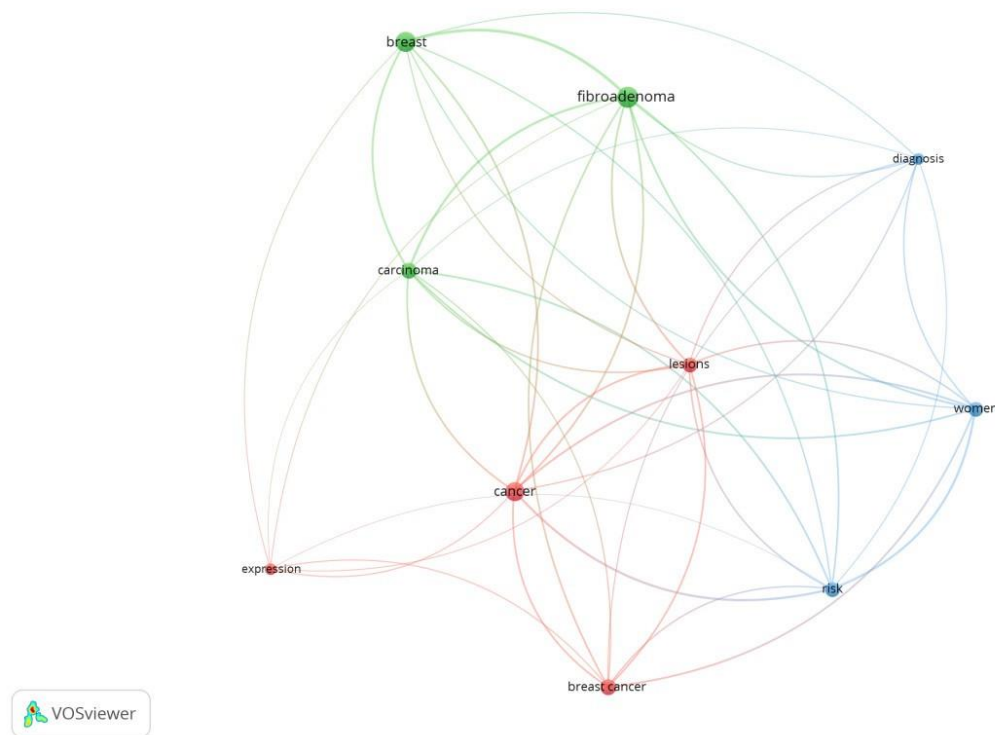
Authors/year	Title	Source	Citations
Dupont et al. (1994)	Long-term risk of breast cancer in women with fibroadenoma	New England Journal of Medicine	240
Delfino et al. (2000a)	Breast cancer, passive and active cigarette smoking and n-acetyltransferase 2 genotype	Pharmacogenetics	46
Delfino et al. (2000b)	Breast cancer, heterocyclic aromatic amines from meat and n-acetyltransferase 2 genotype	Carcinogenesis	80
Kuijper et al. (2001)	Histopathology of fibroadenoma of the breast	American Journal of Clinical Pathology	64
Sklair-Levy et al. (2008)	Incidence and management of complex fibroadenomas	American Journal of Roentgenology	43
El-Wakeel & Umpleby (2003)	Systematic review of fibroadenoma as a risk factor for breast cancer	Breast	44
Kabat et al. (2010)	A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer	Cancer Causes & Control	56

	Exome sequencing identifies highly recurrent med12 somatic mutations in breast fibroadenoma		
Lim et al. (2014)		Nature Genetics	91
Yoshida et al. (2015)	Frequent med12 mutations in phyllodes tumours of the breast	British Journal of Cancer	47
Tan et al. (2016)	Phyllodes tumours of the breast: a consensus review	Histopathology	90
Sawhney et al. (1992)	Epithelial stromal interactions in tumours – a morphologic study of fibroepithelial tumors of the breast	Cancer	

Source: Own elaboration based on research results.

Fibroadenoma, carcinoma, cancer, expression, and lesions were among the most cited key-words in publications (Figure 3).

Figure 3. Co-occurrence of the most cited and most related key-words (1981-2019).



Source: Own elaboration based on research results.

4. CASE REPORT

A 26-year-old single black woman sought specialized medical care in October 2019 due to the presence of a nodule in her right breast for one year. There was absence of pain and

phlogistic sings, but the nodule had recently grown. Clinical history revealed that the patient had no chronic disease, nor history of smoking, alcoholism or use of continuous medication. Menarche occurred at 11 years old and there was no family history of cancer. Complementary examinations were asked after the patient was clinically examined.

Ultrasonography (USG) of the breast was performed on 16th October 2019, revealing the presence of two nodules in her right breast. One nodule was oval-shaped, circumscribed, hypoechoogenic, measuring 3.1 x 1.9 x 2.9 cm, located in parallel to the skin surface at the junction of the upper quadrants of the breast and in 12-hour position (Figure 4). The other nodule was oval-shaped, micro-lobulated, hypoechoogenic, measuring 3.0 x 1.7 x 2.6 cm located at the lower-lateral quadrant of the breast and in 8-hour position (Figure 5). Axillary lymph nodes had usual appearance. Based on the Breast Imaging Reporting and Data System (BI-RADS) classification, examination indicated that the lesion was suspected to be highly malignant and suggested biopsy of the nodule in the 8-hour position.

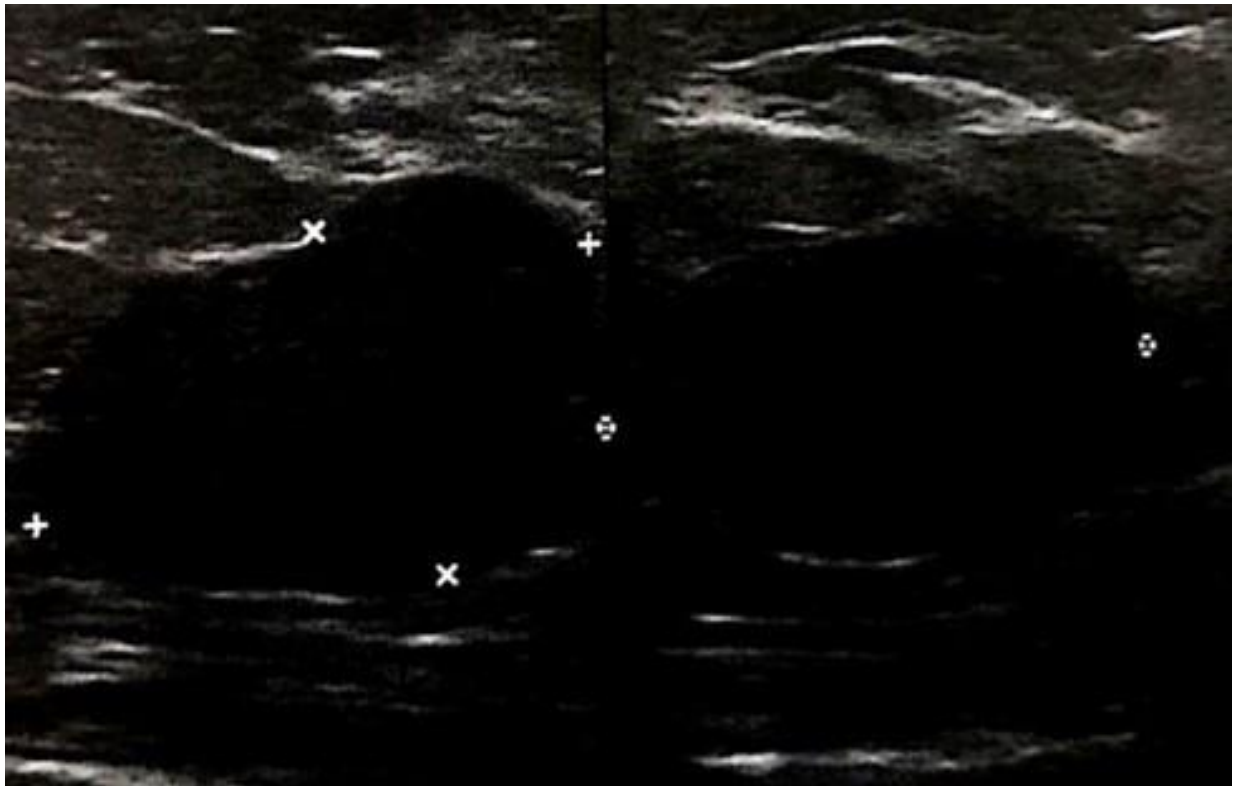


Figure 4. USG of the right breast, showing oval-shaped, circumscribed, hypoechoic nodule, measuring 3.1 x 1.9 x 2.9 cm, located in parallel to the skin surface at the junction of the upper quadrants.



Figure 5. USG of the right breast showing oval-shaped, circumscribed, micro-lobulated nodule, measuring 3.0 x 1.7 x 2.6 cm, located at the lower-lateral quadrant.

Core biopsy of the micro-lobulated nodule was performed on 22nd October 2019. Histological sections revealed presence of benign fibro-epithelial neoplasm compatible with complex FA. (Figure 6).

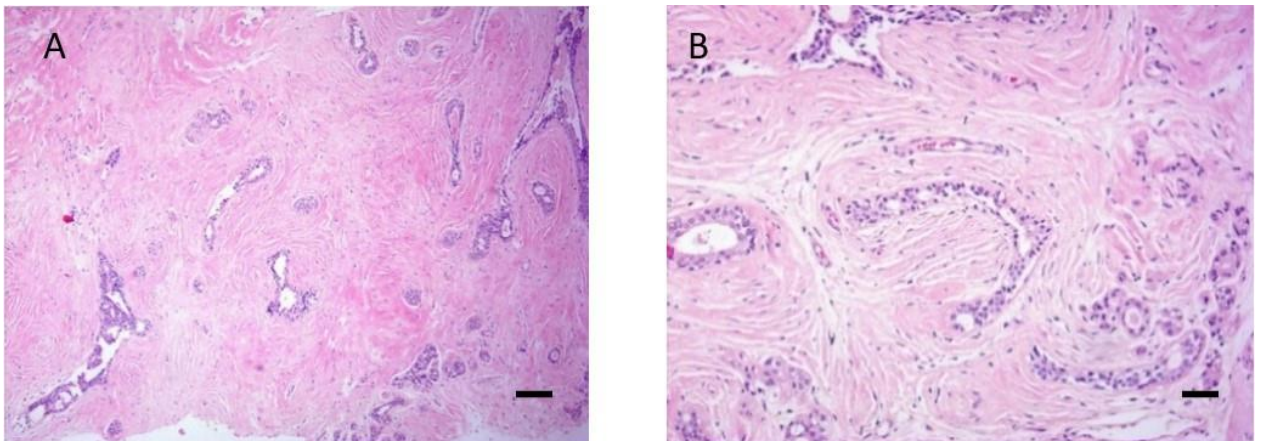


Figure 6. A (100x magnification) and B (400x magnification): Microphotograph of the nodule stained with haematoxylin & eosin, revealing benign fibro-epithelial neoplasm, characterized by ductile proliferation with an intra- and peri-canalicular pattern and collagenised stroma.

After diagnostic confirmation, the patient was referred to an oncological surgeon for evaluation. The surgeon opted for performing two surgeries on different days, due to lack of proximity of the nodules and to avoid necrosis of the papilla with areole incision. The surgeries were held on 1st December 2019 and 21st January 2020. The biopsy was repeated after removal of the nodules, confirming the diagnosis of complex FA.

5. DISCUSSION

After the bibliographic review, high-quality articles indexed on the Web of Science database could be found, and having an overview on the scientific production in the world was possible, showing that there are only 160 studies on fibroadenoma. As to the evolution of publications per year, the first article was published in 1981, and that the number of these studies increased significantly from 1991 onwards, with five publications yearly, on average.

Most studies are published in foreign journals, highlighting the Journal of Ultrasound in Medicine, which has the highest number of published articles. As to the number of published articles by country and according to the author's institutional links, the United States leads the list of studies as they account for almost 30% of all publications. Among the authors with the most cited articles, Dupont *et al.*, Lim *et al.* and Tan *et al.* are highlighted.

In the present clinical case, the patient was 26 years old, which coincided with the most affected age group, as reported in the literature. Nevertheless, one of the FAs found was located in the right breast at the junction of the upper quadrants in 12-hour position, and the other was at the lower-lateral quadrant in 8-hour position, which is not consistent with the usual findings in literature.

Complex FAs are a sub-type of fibroadenoma, presenting one or more pathological characteristics, such as epithelial calcifications, apocrine metaplasias, sclerosing adenoma, and cysts larger than 3 mm. Among the most frequent characteristics, irregular shape, complex echo-structure with anechoic and echogenic components, including non-circumscribed contours, which can be micro-lobulated, indistinct, spiculated, and angular are mentioned. Some characteristics reported in literature coincide with those found in the patient's nodules, such as micro-lobulation (nodule in 8-hour position) and parallel orientation to the skin surface (nodule in 12-hour position), whereas others diverge, such as the presence of more than one nodule.

In the present clinical case, the patient's nodule classified as complex, based on histopathological evaluation, which showed smaller measurements (3.0 x 1.7 x 2.6 cm) compared to those of a simple FA (3.1 x 1.9 x 2.9 cm). The volume of FAs can increase by 16% per month in women younger than 50, whereas in older women the volume increases by 13%, or 20% in all dimensions during six months in women of all ages. Although this growth

does not necessarily mean a process of malignancy, surgical excision is recommended if these dimensions are exceeded⁹.

As to pathogenesis, there is a relation with an increased expression of the BCL-2 gene, which accounts for apoptosis prevention⁵. This maintains the balance between cell proliferation and programmed cell death, which is the mechanism by which cells with damaged DNA are removed without causing any harm¹⁰.

Moreover, MED12 has been reported to be one of the most frequently mutated genes in FAs, located on chromosome Xq13.1. The high frequency of MED12 mutations in fibro-epithelial tumours suggests that it is a somatic gene leading to fibro-epithelial tumorigenesis. Mutations were reported in the exon-2 of MED12 gene, which encodes a protein interacting with proteins CDK8 (human protein kinase), CDK19, CYCC, and MED13. This protein interaction forms a complex for mediating the RNA polymerase II, which participates in the regulation of transcription and consequently in the development of FA. In addition, codon 44 was found to be highly mutated and representing 86% of the mutations of FA¹¹.

The management of younger patients is usually more conservative when clinical, histological, and imaging criteria, including thick-needle aspiration biopsy, suggest a benign lesion. Lesions characterised by BI-RADS 2 follow a screening routine, whereas those characterised by BI-RADS 3 require a six-month ultrasound follow-up if lesions had been ultrasonographically observed, or a mammographic follow-up if lesions had been mammographically observed. FAs with no atypical findings can be monitored with mammography or ultrasound twice a year, for two years and, then once a year⁶.

Performing a percutaneous biopsy is recommended to confirm histological diagnosis if the following findings are present: inconclusive ultrasound findings (BI-RADS 4); evidence of growth trend (clinically and ultrasonographically); new palpable mass during menopause; solid mass found in a patient with risk factors (positive family risk and/or BRCA mutation); and mammography showing mass with suspicious micro-calcifications¹². In this way, excisional biopsy is indicated when histopathological biopsy reveals a high-risk lesion to rule out possible malignancy.

In the present case, ultrasonography showed presence of BI-RADS 4 lesion. In category 4, although lesions did not have the morphological characteristics typically seen in cancer, they may be malignant, thus justifying a biopsy¹³. The diagnosis of complex FA was achieved after analysis of the biopsied material.

Mammography has a sensitivity of 85%-95% and can be used for primary diagnosis of FA, but its specificity is lower. Seen that, other diagnostic methods must be used¹⁴. In the present case, ultrasonography was chosen because young patients present dense breasts, which makes it difficult to visualise nodules on mammogram.

Studies demonstrate that sound-elastography can be used as a complementary diagnosis to evaluate unclear breast masses, such as fibroadenomas, thus contributing to the follow-up and clinical management of patients. However, combining BI-RADS classification with elastography is needed for a more effective management¹⁵.

Treating this pathology can vary depending on the patient's age and nodule's dimensions. In general, simple removal is performed when the nodule is larger than 2 cm. Smaller nodules are only clinically followed up every six months, as well as in patients younger than 25. Removal is indicated only in cases of rapid growth and in women older than 35⁷.

In the case reported, removal of the nodules was indicated due to their dimensions. Because patients diagnosed with complex FAs are 3.1 times more likely to develop invasive breast cancer and because the risk remains high for at least 20 years after diagnosis^{1,6}, a longitudinal follow-up of the patient with ultrasonography was indicated every six months.

6. FINAL CONSIDERATIONS

This present bibliometric literature review has allowed us to discuss on 160 articles, which addressed the theme of complex fibroadenoma on different occasions. From the characterisation and analysis of the above-cited articles, evidence states that there are gaps in the production of knowledge on FAs, because there are only a few studies investigating the theme in depth.

By analysing the bibliometric aspects of scientific production, health care professionals and researchers can understand the characteristics of the published articles. Moreover, further investigations and new studies are extremely necessary as complex FA is still widely unknown by general practitioners in the medical practice.

Clinical case study facilitates a better understanding on complex FAs in various contexts, such as clinical characteristics, imaging examinations, and histopathological aspects, which can help the health care professional to make the pathology diagnosis.

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