GS GLAND SURGERY
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First external peer review

Reviewer A

In this manuscript, the authors reported a case report of a patient with bilateral desmoid tumors of the breast, which showed spontaneous regression after almost 3 years of active surveillance. According to the journal guideline, a case report requires exceptional interest and novelty for publication. Thus, the authors might want to stress new findings that have clinical impact on breast oncology field or may change clinical practice. A review of previously-published breast desmoid fibromatosis with active surveillance and/or an addition of molecular/genomic analysis of the bilateral tumors might help the authors to identify clinical significance of this case report.

Specific comments

1) Desmoid fibromatosis

The authors might want to call the tumor "desmoid fibromatosis". This is because "desmoid fibromatosis" can be more official histological name than "desmoid tumor" according to the 5th edition of the WHO classification of breast tumors.

Reply: We have modified our text as advised.

Changes in the text: "Desmoid tumor" was replaced with "Desmoid-type fibromatosis". The abbreviation "DT (desmoid tumor)" was replaced with "DF (desmoid-type fibromatosis)". The abbreviation "BDT (breast desmoid tumor)" was replaced with "BDF (breast desmoid-type fibromatosis)". See the title and the whole manuscript.

2) Desmoid fibromatosis is NOT a benign tumor

The authors stated that desmoid fibromatosis is a benign tumor, but they might want to classify this tumor as "intermediate, locally aggressive" according to the WHO classification of soft tissue tumors.

Reply: We have modified our text as advised. Therefore, we added this reference: Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. Pathologica. 2021;113(2):70-84. doi:10.32074/1591-951X-213

Changes in the text:

- "It is both benign since it has no metastatic potential and aggressive because of local invasion." was replaced with "It is classified as intermediate tumor because it is locally aggressive but has no metastatic potential." see "abstract" page1, line12-13.
- "benign mesenchymal tumor arising from musculoaponeurotic structures" was replaced with "locally aggressive and nonmetastasizing mesenchymal tumor arising from musculoaponeurotic structures" see "introduction" page 1 line 36-37.

- "BDT is a very rare, deeply infiltrative, benign mesenchymal tumor." was replaced with "BDF is a very rare, locally aggressive mesenchymal tumor." See "conclusion" page 6, line 232.

3) Radiological images

3-1) Mammography (Figure 1)

A mass in the right breast and an architectural distortion in the left breast are both unclear. The authors might want to show enlarged images of the lesions, the spot compression images, and/or the craniocaudal (CC) views in addition to the MLO views.

Reply: Digital tomosynthesis images and close-up images of the lesions were added to "figure 1". We didn't add craniocaudal views as they were not performed in order to limit radiation, as the patient is young (20 years old).

Changes in the text: see "figure 1".

3-2) Ultrasonography (Figure 2)

The authors might want to add a scale to each of the images. The image of the right tumor after active surveillance looks larger than the image of the tumor at initial diagnosis.

Reply: A scale was added to each image as advised.

Changes in the text: see "figure 2".

3-3) MRI

The authors might want to rethink if all of the three sequences are essential for this case report. I feel that only one image (C) is enough for the case report. Moreover, the authors might want to show extent of the tumors by adding arrows on the image(s).

Reply: We only kept a subtraction image for the case report. We did not show the tumors on the image as they cannot be identified due to a "background parenchymal enhancement" effect. The images were reviewed by several radiologists.

Please note that another image from the same sequence as image (C) was chosen for quality purpose.

Changes in the text: see "figure 4" and "Case presentation" page 2, line 84-86 for more detail.

3-4) CT

The authors might want to show extent of the tumors adding arrows on the image.

Reply: We did not show the tumors on the image as they are not differentiable from the mammary glands. The main purpose of the CT scan is to perform an evaluation of the local extension of the tumor but not to measure it. The images were reviewed by 3 radiologists-senologists.

Figure 5 description was modified accordingly to prevent confusion.

Changes in the text: "**Figure 4** Chest computed tomography with iodinated contrast, arterial phase. The soft tissue

window shows bilateral hypodense breast tumors infiltrating the underlying deep fatty tissues

and coming in contact with the pectoral muscles. No muscular infiltration was objectivated." was replaced with "**Figure 5** Chest computed tomography with iodinated contrast (Omnipaque® 350 mg I/ml), arterial phase. The soft tissue window shows hypodense breast tumor tissue infiltrating the underlying deep fatty tissues bilaterally and coming in contact with the pectoral muscles but without infiltrating it." Please see "figure5".

4) Pathological findings

4-1) Images

The authors might want to show H&E and immunohistochemical images of the bilateral tumors. Especially, nuclear staining of β-catenin is desirable for the diagnosis of desmoid fibromatosis.

Reply: H&E and immunohistochemical images of the bilateral tumors were added.

Changes in the text: see "figure 3".

4-2) β-catenin

The authors might want to specify the staining pattern of β-catenin in the text. Nuclear staining, not cytoplasmic staining, of β-catenin is important for the diagnosis of desmoid fibromatosis.

Reply: We specified the staining pattern of β-catenin as advised.

Changes in the text: "The anatomopathological analysis argues for a bilateral desmoid fibromatosis with negative hormone receptors, weak Ki67 expression (< 1%), weak actin positivity and strong β-Catenin positivity" was replaced with "The anatomopathological analysis argues for a bilateral DF with negative hormone receptors, weak Ki67 expression (< 1%), weak actin positivity and strong nuclear β-Catenin positivity (Figure 3)." Please see "case presentation" page 2, line 79-81 and figure 3.

5) Tables 1–3 are unnecessary

Details of the BI-RADS classifications and the RECIST classification are unnecessary for this caser report. The authors might want to cite the references and delete Tables 1, 2 and 3.

Reply: Tables 1,2 and 3 were deleted and references are cited.

Changes in the text: See "figures and tables" and references 24 and 31.

Reviewer B

The article is a case report of a patient with bilateral breast desmoid tumors placed on active surveillance leading to spontaneous regression of the tumors. The case is well described, including an elegant portrayal of the physical examination and sufficient supporting radiological images. The discussion is updated and pertinent. Although the case does not bring any novelty, it is educational and illustrates how active surveillance can lead to excellent outcomes. However, there are minor points that the authors need to address:

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1. The authors state that there are “very few cases of bilateral breast desmoid tumor” (Line 27). If possible, they should be more specific and cite them.
Some cases include:
PMID: 27578999, 21708372, 21629058, 15896828, 20133249, 30008823, 32590455
Of note, the fact that 1 out of 132 cases of breast desmoid tumors is bilateral gives an idea of its incidence (32590455)
Reply: We modified the text as advised and we cited references.
Changes in the text:

- “Here is reported a rare clinical case of bilateral BDTs in a 20-year-old woman” was replaced with “Here is reported a clinical case of bilateral BDF in a 20-year-old woman, which is rare as only few cases of bilateral BDF have been published so far[9,13-18].” See “introduction”, page 2, line 58-59, references 9 and 13-18.
- “Bilateral cases are rare and account for about for about 1 % of BDF[9]” was added to the text. See “introduction”, page 1, line 42-43, reference 9.

2. Many aspects of this phrase are hard to understand or contradictory:
“Although only 5 to 6 cases per million inhabitants per year are recorded, DT implies an important diagnostic challenge and requires appropriate management.” (Line 48-49)
It is unclear why the rarity of DT contrasts (“although”) with DT being a diagnostic challenge. Do the authors mean something like: “There are only 5 to 6 DT cases per million people per year. Due to its rarity, DT presents an important diagnostic challenge”? Also, I don’t understand what the authors mean by “requires appropriate management.” By default, all conditions require appropriate management.
Reply: We modified the text as advised.
Changes in the text: “Although only 5 to 6 cases per million inhabitants per year are recorded, DT implies an important diagnostic challenge and requires appropriate management.” was replaced with “There are only 5 to 6 cases of DF per million inhabitants per year. Therefore, this rare tumor presents an important diagnostic challenge” please see “introduction” page 2 line 50-51.

3. Please explain “An additional magnetic resonance imaging (MRI) with contrast was performed but turned out interpretable due to background parenchymal enhancement.” (Line 80-81)
From the images attached, it seems that the desmoid tumors can be visualized on the MRI and the CT scan.
Reply: The tumors are not differentiable from the rest of mammary glands because of “background parenchymal enhancement”. This phenomenon is due to normal fibroglandular tissue enhancement on breast MRI and is influenced by exogenous and endogenous hormone levels. It can alter MRI reading and interpretation.
Changes in the text: See “figure 4” and “Case presentation” page 2, line 84-86, reference 19.

A reference is cited (Liao GJ, Henze Bancroft LC, Strigel RM, et al. Background parenchymal enhancement on breast MRI: A comprehensive review. J Magn Reson Imaging. 2020;51(1):43-61. doi:10.1002/jmri.26762)

5. "The main risk factors for DT are trauma and surgery and it is estimated in literature that 30% of DTs occur in such context" (Line 46-47)
Particularly in breast desmoid tumors, breast implants consist of an important risk factor. The authors should consider mentioning it (PMID: 34453383)
Reply: We modified the text as advised and included the suggested reference.
Changes in the text: "Breast implants have also been identified as another important risk factor." See "introduction", page 2, line 48-49, reference 11.

6. The authors rightfully mention that an expert pathologist should review the histology for desmoid tumors. This is evidenced by the fact that 30% of desmoid tumors have their diagnosis changed after revision (PMID: 32590455). They also rightfully mention different pathologies that are easily mistaken on histology with desmoid tumors. Due to all those facts, it is crucial to have a histological image of the desmoid tumor described in the case. This will help guarantee to the reader that the case described is indeed a desmoid tumor. Also, on the histology of the case, the authors should mention the morphological description instead of just the reporting immunohistochemistry.
Reply: Histological images and description of DF were added.
Changes in the text: See "figure 3" and its description.

7. The recurrence rates for DT can vary in the literature, but definitely, DT doesn't "inexorably recur." Please change: "DT tends inexorably to locally infiltrate tissues and to recur" (Line 50)
Reply: We modified the text as advised.
Changes in the text: "Indeed, despite its inability to metastasize, DT tends inexorably to locally infiltrate tissues and to recur." was replaced with "Moreover, despite its inability to metastasize, DF tends to locally infiltrate tissues and to recur[1,2,3,4,6,7,8,9]." See "introduction" page 2 line 51-52.

8. Please place arrows (or any other form of demarcation) on the tumors on the CT and MRI scans. If possible, please also include measurements.
Reply: We did not identify the tumors on the CT and MRI because they are not differentiable from the rest of mammary glands. Images have been reviewed by 3 seno-radiologists.
Changes in the text: none.

9. The image A on the US is hard to see. Is it possible to have a better/brighter image?
Reply: Image A of figure 2 has been replaced with a brighter one. Please be aware that we changed our ultrasound scanner from a Philips IU15 of 2008 to a Supersonic Aixplorer Mach 30 of last generation between the diagnosis' images and the 2.7 years follow-up images.

Changes in the text: see “Figure 2”.

10. Image D on the US reports two diameters. In contrast, all the rest are reporting only the largest diameter. Please keep the largest diameter for consistency.
Reply: As advised, only the larger diameter was kept for image D.
Changes in the text: see “Figure 2”.

10. Why does the CT image shows an early-arterial phase instead of a late venous phase? Is DT better visualized at arterial phases? If so, please cite.
Reply: CT was only performed with a contracted acquisition (Omnipaque 350) at the systemic arterial phase to limit irradiation as the patient is young (20 years old). The main purpose of the CT scan is to perform an evaluation of the local extension of the tumor but not to measure it.. The images were reviewed by 3 radiologists-senologists.
Changes in the text: See “Figure 5”.

11. Please explain what the authors mean with:
“In the absence of pathognomonic lesion and considering the limited number of mammographic images in such a young patient, the mammogram interpretation hinges on the clinical context and breast examination” (Line 127-129)
Consider completely rephrasing it, as it is very hard to understand it.
Reply: We modified the text as advised.
Changes in the text: “In the absence of pathognomonic lesion and considering the limited number of mammographic images in such a young patient, the mammogram interpretation hinges on the clinical context and breast examination.” was replaced with “Indeed, due to the young age of the patient, a limited number of mammographic images were taken. It is why other techniques were preferred for the diagnosis of DF.” Please see “case presentation”, page 3-4, line 130-132.

12. “Currently, initial medical management has not shown any advantage in terms of PFS compared to AS and is therefore not recommended” (Line 170)
Active medical treatment does have better PFS survival than AS. Although, it doesn’t have any clinical advantage, as an initial AS approach does not appear to influence the efficacy of subsequent treatments when needed. Even the cited reference reports: “The European paediatric Soft tissue sarcoma Study Group (EpSSG) showed a difference in the 5-year PFS between the observation (n = 54) and the chemotherapy group (n = 53) (27% and 43%, respectively)”.
Please rephrase the passage to reflect the benefit is in clinical outcomes (less toxicity, a better quality of life, etc.) rather than strictly PFS.
Reply: We modified the text as advised.
Changes in the text: “Currently, initial medical management has not shown any advantage in terms of PFS compared to AS and is therefore not recommended” was replaced with “Currently, initial medical treatment has not shown any advantage in terms of PFS compared to AS. Moreover, AS has a greater benefit in terms of clinical outcomes : less toxicity and morbidity,

better quality of life. Initial medical treatment is therefore not recommended in the first-line setting." See "Discussion", page 4-5, line 173-176.

13. "During AS, if the disease progresses according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Table 3) or after noticing disease progression on two occasions or worsening of symptoms; medical or surgical management should be initiated." This statement about when to switch to active treatment differs slightly from the reference (working group statement). Please adjust/summarize accordingly

Reply: We modified the text as advised.

Changes in the text: "During AS, if the disease progresses according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Table 3) or after noticing disease progression on two occasions or worsening of symptoms; medical or surgical management should be initiated." was replaced with "If radiological disease progression occurs or if symptoms' intensity increases during AS, evaluated by at least two further assessments and possibly not before one year from diagnosis in the absence of fulfilled RECIST progression criteria, medical or surgical management should be initiated. See "Discussion", page 5, line 181-184.

14. While discussing the treatment options, only peg-doxorubicin is mentioned for aggressive tumors. Since doxorubicin + dacarbazine is also frequently used, I suggest changing to "Anthracycline-based regiments" to be more encompassing.

Reply: We modified the text as advised.

Changes in the text: "For more aggressive diseases, chemotherapy with pegylated doxorubicin can be considered." was replaced with "For more aggressive diseases, chemotherapy with anthracycline-based regiments can be considered". See "discussion", page 5 line 192.

Also, although the sorafenib trial is more robust, pazopanib has good scientific evidence (desmopaz trial NCT01876082). Please include it in the discussion.

Reply: We included pazopanib in the discussion and the reference was cited.

Changes in the text: "The randomized, open-label, phase 2 DESMOPAZ trial evaluated Pazopanib (800mg per day) versus intravenous chemotherapy (vinblastine-methotrexate) in progressive DF setting. The authors showed that the proportion of patients who had not progressed at 6 months was 83.7 % and 45% with pazopanib and chemotherapy, respectively[10,34]" was added to "Discussion", page 5, line 202-205.

15. "However, CTNNB1 exon 3 mutation is less common (40-50 %) in BDT than in other tumor sites" (Line 156-157). Please cite a reference for this statement. A good reference would be PMID: 32590455, although their rate would be 65-77% (instead of 40-50%).

Reply: This reference initially cited was " Duazo-Cassin L, Le Guellec S, Lusque A, et al. Breast desmoid tumor management in France: toward a new strategy. Breast Cancer Res Treat. 2019;176(2):329-335." but we added PMID: 32590455 as another reference.

Changes in the text: "However, CTNNB1 exon 3 mutation is less common (40-50%) in BDF than in other tumor sites." was replaced with "However, CTNNB1 exon 3 mutation is less

common (65-77%) in BDF than in other tumor sites (88 %)[8,9].” See “Discussion” page 4, line 158-159.

16. “She was also referred to a genetic consultation and molecular analysis did not reveal any mutation of APC or MUTYH genes.” (Line 99-100)
The authors state that the patient was sent for genetic analysis. Did the authors perform a somatic or a tumor analysis? If tumor analysis, please inform the mutation findings. If somatic, please state it was a somatic mutation analysis.
Reply: Molecular analysis searched for a germline mutation of APC or MUTYH gene.
Changes in the text: “She was also referred to a genetic consultation and molecular analysis did not reveal any mutation of APC or MUTYH genes, which does not argue for FAP or MUTYH-associated polyposis (MAP).” was replaced with “She was also referred to a genetic consultation and molecular analysis did not reveal any germline mutation of APC or MUTYH genes, which does not argue for FAP or MUTYH-associated polyposis (MAP).” See “Case presentation”, page 3, 101-103.

17. Genetic analysis is not required for the diagnosis of DT.
“Diagnosis should also be confirmed through genetic analyses searching for CTNNB1 or FAP mutations.” (line 226-227)
Genetic analysis can supplement histological evaluation and might be helpful in case of diagnostic doubt. It is not a fundamental part of the diagnosis. Also, mutation analysis currently doesn’t play a definitive role in the management as it is not predictive of progression nor of systemic therapy response (PMID: 35180772).
This statement steers providers to request a genetic analysis on all DT patients. This can generate an unnecessary financial burden, especially on the health care of mid-income countries.
Reply: We modified the text as advised and reference was added.
Changes in the text:

- “Diagnosis should also be confirmed through genetic analyses searching for CTNNB1 or FAP mutations.” was replaced with “histological diagnosis can also be supplemented by genetic analyses searching for CTNNB1 or FAP mutations in case of diagnostic doubt” See “conclusion”, page 6, line 235-237.
- “Finally, identifying mutations might be helpful in case of diagnostic doubt but mutation status does not predict systemic therapy responses.” was added. See “discussion”, page 4, line 160-161.

18. English style revisions
Although grammar and spelling are mostly correct, there are some hard-to-read sentences and unusual word choices up to the Discussion section. The article would benefit from a review from a native English speaker.
Some examples include:

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The word “iconographic” seems to be used throughout the manuscript with the meaning of “radiologic.” “Radiologic” is a more commonly used word in this context.
Reply: We modified the text as advised.
Changes in the text: “iconographic” was replaced with “radiologic” through the whole manuscript.

“Active surveillance phase” should be substituted for simply “active surveillance.”
Reply: We modified the text as advised.
Changes in the text: “Active surveillance phase” was replaced with “Active surveillance”. See “abstract”, page 1, line 18 and “case presentation, page 3, line 98.

“Clinical case” should be substituted by just “case.” The context is sufficient to understand it is a clinical case rather than a radiological, histological, etc.
Reply: We modified the text as advised.
Changes in the text: “Clinical case” was replaced with “Case”. See “abstract”, page 1, line 22, line 25 and “introduction”, page 2, line 59.

“Bilateral breast desmoid tumor” should be substituted for the plural form “tumors” (bilateral)
Reply: We decided to replace “breast desmoid tumor” with “breast desmoid-type fibromatosis” as advised by reviewer B.
Changes in the text: “Desmoid tumor” was replaced with “Desmoid-type fibromatosis”. The abbreviation “DT (desmoid tumor)” was replaced with “DF (desmoid-type fibromatosis)”. The abbreviation “BDT (breast desmoid tumor)” was replaced with “BDF (breast desmoid-type fibromatosis)”. See the title and the whole manuscript.

This sentence is hard to read: “Its diagnosis is often difficult because it shares many clinical and iconographic aspects with breast carcinomas, making biopsy and anatomopathological study essential to the diagnosis, sometimes supplemented by genetic analysis.”
Reply: We modified the text as advised.
Changes in the text: “Its diagnosis is often difficult because it shares many clinical and iconographic aspects with breast carcinomas, making biopsy and anatomopathological study essential to the diagnosis, sometimes supplemented by genetic analysis.” was replaced with “ “BDF diagnosis is often difficult because it shares many clinical and iconographic aspects with breast carcinomas, and therefore relies on anatomopathological analysis which may be supplemented by genetic analysis." See “Abstract”, page 1, line 13-15.

Reviewer C

I commend the authors on a very well written manuscript.
A few questions and suggestions:

1. There are a few "blank" spaces in the body and Footnote of the manuscript. Are these omissions purposeful or made in error? (example: last sentence of Introduction)

Reply: Those blank spaces have been removed from the manuscript.
Changes in the text: see “introduction” and “footnote”.

2. Page 2 line 81 states the MRI turned out "interpretable". If I understood correctly, it was not interpretable. Needs correction..

Reply: The MRI is indeed not interpretable, it was an error.
Changes in the text: “An additional magnetic resonance imaging (MRI) with contrast was performed but turned out interpretable due to background parenchymal enhancement (Figure 4).” was replaced with “An additional magnetic resonance imaging (MRI) with contrast was performed but turned out uninterpretable due to background parenchymal enhancement (Figure 4).” Page 2, line 83.

3. I am not sure that Table 1 and 2 are necessary or really add much to the submission. These are accepted standard breast imaging descriptions. I would omit these and keep the remaining graphics.

Reply: Tables 1,2 and 3 were deleted.
Changes in the text: see “figures and tables”.

Again, I appreciate the authors' work on this submission and look forward to its addition to the body of literature on this topic.

For editor
a couple minor errors noted and a couple of suggestions. Otherwise well written manuscript that I would consider worthy of publication after these minor revisions.

Second external peer review

Reviewer A
Pathological images:
The authors newly showed intermediate-magnification views of H&E staining and β-catenin immunostaining of the bilateral desmoid fibromatosis. However, the authors might want to add high-magnification view as small inset to each image, so that the readers easily observe the morphological features and nuclear staining pattern of β-catenin of the bilateral desmoid fibromatosis.
Reply: We added 400-fold magnification for each image as advised.
Changes in the text: See figure 3.