Intracranial solitary fibrous tumors/hemangiopericytomas: first report of malignant progression

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OBJECTIVE Meningeal solitary fibrous tumors/hemangiopericytomas (MSFTs/HPCs) are rare intracranial tumors resembling meningiomas. Their classification was redefined in 2016 by the World Health Organization (WHO) as benign Grade I fibrohyaline type, intermediate Grade II hypercellular type, and malignant highly mitotic Grade III. This grouping is based on common histological features and identification of a common *NAB2-STAT6* fusion.

METHODS The authors retrospectively identified 49 cases of MSFT/HPC. Clinical data were obtained from the medical records, and all cases were analyzed according to this new 2016 WHO grading classification in order to identify malignant transformations.

RESULTS Recurrent surgery was performed in 18 (37%) of 49 patients. Malignant progression was identified in 5 (28%) of these 18 cases, with 3 Grade I and 2 Grade II tumors progressing to Grade III, 3–13 years after the initial surgery. Of 31 Grade III tumors treated in this case series, 16% (5/31) were proved to be malignant progressions from lower-grade tumors.

CONCLUSIONS Low-grade MSFTs/HPCs can transform into higher grades as shown in this first report of such progression. This is a decisive argument in favor of a common identity for MSFT and meningeal HPC. High-grade MSFTs/HPCs tend to recur more often and be associated with reduced overall survival. Malignant progression could be one mechanism explaining some recurrences or metastases, and justifying long-term follow-up, even for patients with Grade I tumors.

KEY WORDS hemangiopericytomas; solitary fibrous tumor; *NAB2-STAT6*; oncology

Meningeal solitary fibrous tumors/hemangiopericytomas (MSFTs/HPCs) are rare intracranial tumors that resemble meningiomas on clinical presentation and imaging and are frequently confused. Fibrohyaline Grade I tumors (MSFTs) are histologically different from hypercellular meningeal hemangiopericytomas (MHPCs), which may be Grade II or Grade III, based principally on the number of mitoses. This is the reason why, historically, these lesions have been described with different nomenclature. However, MSFTs and HPCs share a common morphological pattern, with typical "staghorn" vascularization, and a common recently identified pathognomonic *STAT6* nuclear expression.[3,16,18] Logically, based on their common molecular signature, mechanism of tumorigenesis, and expression of the NAB2-STAT6 fusion protein,[4,15] they have recently been regrouped in the 2016 WHO classification.[9]

Fusion of *NAB2* and *STAT6* genes, which are located in the 12q13 region and are transcribed in opposite directions, has been identified in all types of solitary fibrous tumors, intracranial and peripheral, inducing tumor initiation.[4,15] NAB2 protein is an intranuclear transcriptional modulator for EGR (early growth response) zinc finger transcription factors. STAT6 protein, mostly expressed in the cytoplasm, acts as a signal transducer and a transcription activator. By acquiring this activation domain, NAB2 converts its repressing activity into transcriptional activation, which explains the tumorigenicity of the NAB2-STAT6 fusion

ABBREVIATIONS HPC = hemangiopericytoma; MHPC = meningeal HPC; MSFT = meningeal solitary fibrous tumor.

protein,[4,15] now diagnosed by routine STAT6 nuclear immunopositivity.[16,19]

The clinical evolution of patients presenting with MSFT/HPC is unpredictable, as local recurrence may occur in 20% to 85% of cases and somatic metastasis in 12% to 36%,[5,10,11] and treatment, based on surgery and radiotherapy/radiosurgery, is thought to slow recurrence without curing the disease.[6,17]

Despite much effort given to predicting the clinical behavior of MSFT/HPC based on pathological features, no clear aggressiveness factor has been identified in published series, neither histological—Ki-67 labeling index or grading[5,13]—nor molecular.[7]

According to the new 2016 WHO classification, MSFT/HPC are now divided into 3 grades: Grade I comprises fibrous tumors that typically harbor no mitosis; Grades II and III are hypercellular tumors and differ depending on the mitosis count (< 5 or ≥ 5 mitoses per 10 high-power fields [×400 magnification], respectively).[9]

The connection between Grades I, II, and III has not been elucidated, and it is not clear whether tumors can progress into higher grades. No case of progression has been described until now. As a comparison, we know that meningiomas, which are also meningeal tumors and whose time course seems quite similar to that of MSFT/HPC, can progress to malignancy: 14% to 29% of recurrent benign meningiomas transform into atypical or malignant ones, and 26% to 33% of atypical ones recur as malignant tumors.[1]

We reviewed a local series of cases involving patients who underwent surgery for MSFT/HPC, confirmed the diagnosis with STAT6 immunohistochemistry, classified the tumors according to the 2016 WHO grading, and analyzed the clinicohistological patterns of the cases. We found 5 cases of MSFT/HPC having progressed from Grade I or II to Grade III at the time of local recurrence, an observation that had never been described before.

Methods

Patients who underwent surgical removal of an intracranial MSFT/HPC in the Neurosurgery Department of Pitié Salpêtrière Hospital, Paris, between 1990 and 2016 were identified retrospectively. Collection of patient samples and clinicopathological information was undertaken with patient informed consent and hospital ethics board approval. The patients' clinical history of the patients was obtained from their medical records. Immunochemistry for STAT6 (ABCAM, clone YE361, 1/400) and Ki-67 (DAKO, clone MIB-1, 1/50) was also performed for all cases. The mitotic count and the Ki-67 labeling index were determined in 10 fields in the most actively proliferating areas of the tumors. Exclusion criteria were the absence of STAT6 expression and the impossibility of performing STAT6 immunochemistry on the available pathological samples, because MSFT/HPC could not be diagnosed with certainty in those cases. All diagnoses and grading were reviewed according to the 2016 WHO classification by a senior neuropathologist (K.M.) and a junior neurosurgeon (C.A.).

Results

Population

Between 1990 and 2016, 49 patients were operated on for intracranial MSFT/HPC with 93 surgical procedures. The patients' mean age (± SD) at the time of surgery was 51 ± 7 years (range 17–82 years).

Grading

At the time of the first operation, 15 tumors (31%) were Grade I, 9 (18%) Grade II, and 25 (51%) Grade III (Fig. 1). Five patients (10%) showed malignant progression of their MSFT/HPC: 3 lesions evolved from Grade I to Grade III, and 2 from Grade II to Grade III.

Tumor Recurrence

Thirty patients were operated on once, and 18 patients (37%) were operated on more than once (i.e., underwent at least 1 operation for recurrent tumors). Recurrence occurred 1–21 years after the first surgery (median 4.7 years). Among the 18 cases in which operations were performed for treatment of recurrent tumors, 5 Grade I or II tumors (28%) had transformed into Grade III tumors (Fig. 1) after 3–13 years. The 13 others remained stable (1 Grade I, 2 Grade II, and 10 Grade III). This population is summarized in Table 1 and an illustrative radiological case is described in Fig. 2 (Case 1).

Metastases

Five patients (10%) developed symptomatic extracranial metastases, located in the bones, liver, or lungs, but no systematic screening was performed. One patient with metastatic disease had a Grade II tumor, 3 had Grade III tumors, and the last patient had a Grade II tumor that transformed into Grade III, with the metastasis diagnosed after malignant progression (Case 5).

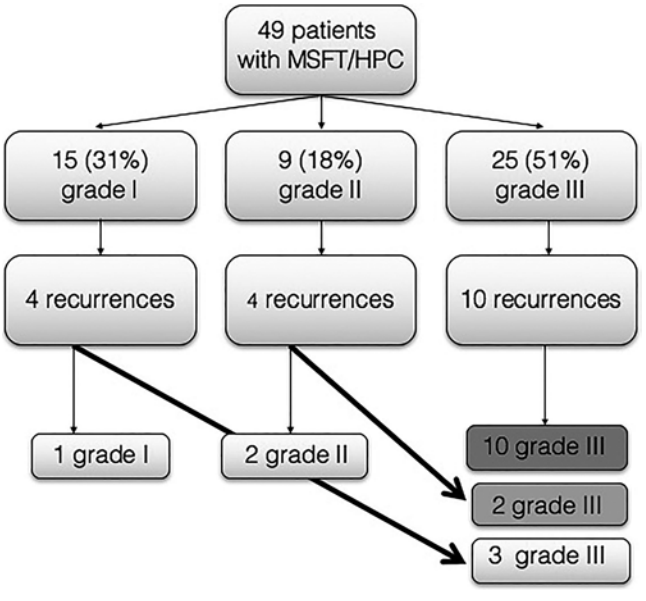

FIG. 1. Flowchart of 49 patients operated on for intracranial MSFT/HPC. Of the recurring tumors, 5 progressed from Grade I or II to Grade III.

TABLE 1. Clinical and histological description of 5 cases of progressing MSFT/HPC

Case No. & Op	Pt Sex	Location	Pt Age (yrs)	Time to Recur (yrs)	RT Before Recur?	Grade	Hypercellular?	Fibrohyaline Aspect?	Necrosis?	Mitoses (per 10 hpfs)	Ki-67	Mets
1	M	Lt parasag parietal convexity		10	Yes							None
Initial op			19			I	No	Yes	No	0	3%	
Recur			29			III	Yes	No	No	12	20%	
2	F	Lt parasag frontal convexity		6	No							None
Initial op			65			I	No	Yes	No	1	2%	
Recur			71			III	Yes	Yes	No	14	NA	
3	F	Orbit		13	No							None
Initial op			44			I	No	Yes	No	0	NA	
Recur			57			III	Yes	No	No	11	20%	
4	M	Lt parasag FP convexity		12	Yes							None
Initial op			37			II	Yes	No	No	1	8%	
Recur			49			III	Yes	No	Yes	6	20%	
5	F	Lt temp convexity & cerebellar tent		3	No							Bone
Initial op			44			II	Yes	No	No	2	5%	
Recur			47			III	Yes	No	Yes	20	15%	

FP = fronto-parietal; Ki-67 = Ki-67 labeling index; Mets = metastases; NA = not available; parasag = parasagittal; Pt = patient; Recur = recurrence; RT = radiotherapy; temp = temporal; tent = tentorium.

* The initial grade of I or II is defined by the fibrohyaline or hypercellular aspect. Grade III is defined by ≥ 5 mitoses per 10 ×400 fields.

Malignant Progression

Two patients underwent radiation therapy before malignant progression. The pathological evolution of 2 progressing cases (Grade I to Grade III in Case 1 and Grade II to Grade III in Case 5) is illustrated in Fig. 3. Among the 31 nonrecurrent tumors, 11 were Grade I, 5 were Grade II, and 15 were Grade III. Overall, we analyzed 31 Grade III tumors, among which 5 (16%) proved to be malignant progressions from lower-grade tumors.

Discussion

Surprisingly, no case of malignant progression of MSFT/HPC has been described previously in the literature, probably because tumors have not been systematically reexamined at recurrence in any previous series. In our series of 49 cases, 18 patients were found to have local recurrences, and in 5 (28%) of these cases, the lesions had transformed into higher-grade tumors.

Reporting the first cases of MSFT/HPC malignant progression has a nosological impact on the classification of these tumors, consistent with the reunification of MSFT and HPC in the recent 2016 WHO classification.[9] Indeed, MSFT and HPC have been grouped on the basis of an overlapping histological appearance,[3,9,19] which strongly suggests a continuum between the 2 types, and they share common prognosis-related factors.[21] Highlighting a common genetic event also supports a common identity, but does not prove it, as a single genetic event can be associated with different tumors; for instance, *NF2* mutations are found in meningiomas, schwannomas, and ependymomas, but this does not call into question their difference. Reporting cases in which MSFT Grade I can progress and

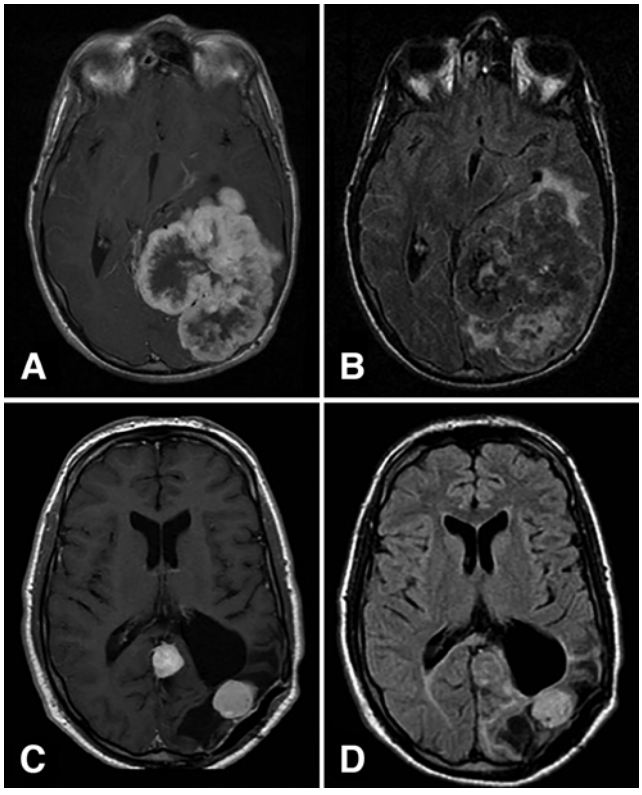

FIG. 2. Case 1. MR images obtained before initial surgery (A and B) and at recurrence with progression (C and D). **A and B:** Axial contrast-enhanced T1-weighted (A) and FLAIR (B) MR images showing a voluminous left parieto-occipital Grade I MSFT/HPC. **C and D:** Axial contrast-enhanced T1-weighted (C) and axial FLAIR (D) images showing nodules of a Grade III MSFT/HPC. Analyzing the tumor and peritumoral edema on brain MRI did not help in predicting the malignant progression.

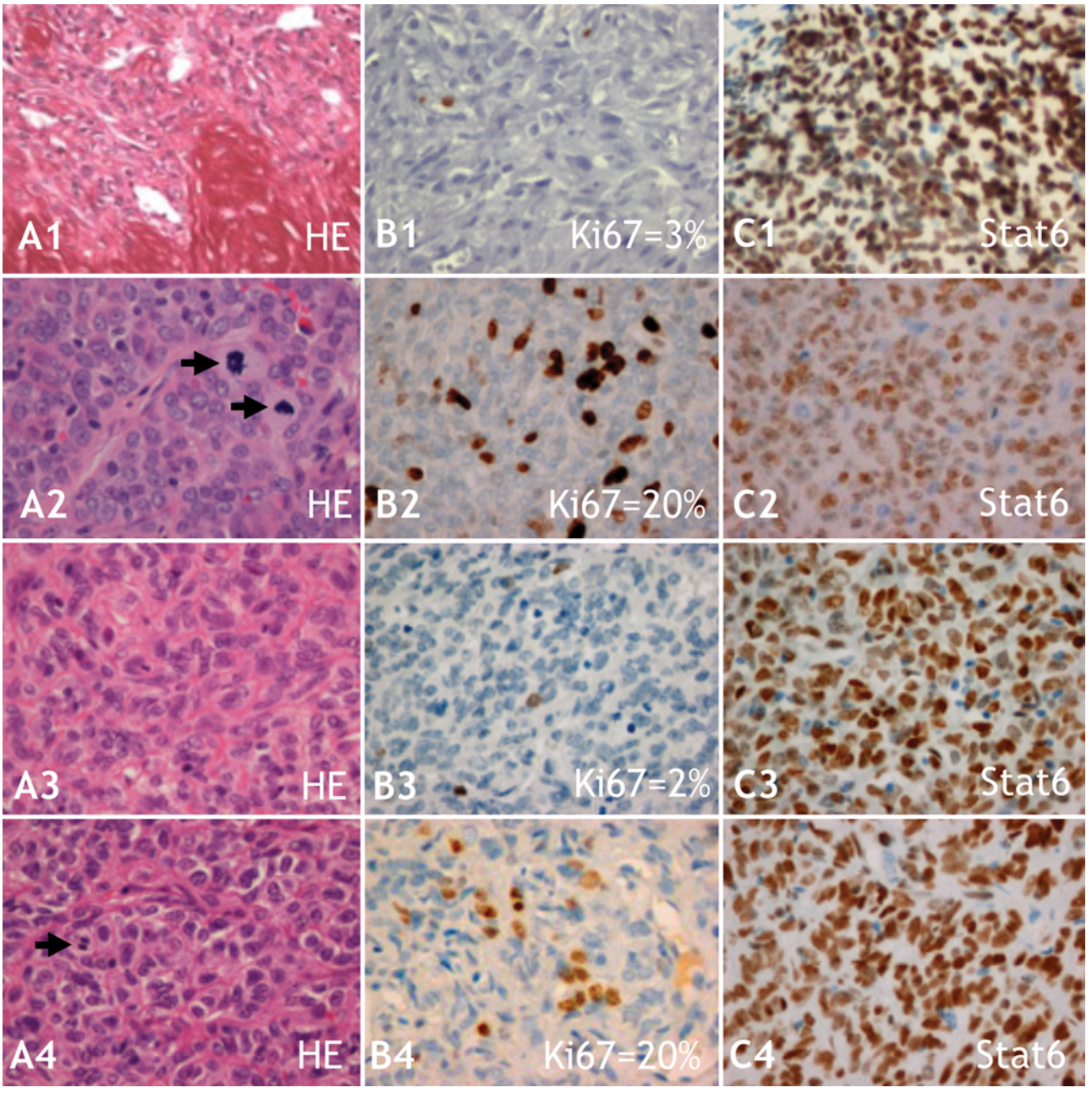

FIG. 3. Photomicrographs of stained specimens of progressing tumors demonstrating pathological changes. The upper 2 rows show specimens from Case 1, and the lower 2 rows show specimens from Case 5. The section in A1 was stained with Sirius red for collagen as well as with H & E. All other panels are stained as indicated on the images. The tumor in Case 1 was initially a Grade I highly collagenous lesion with relatively low cellularity, tumoral cells with spindle-shaped nuclei and scant eosinophilic cytoplasm (**A1**), and a low Ki-67 proliferation index (**B1**); it became a hypercellular (**A2**) and highly mitotic (**A2** *arrow* and **B2**) Grade III tumor at recurrence. The tumor in Case 5 was initially a highly cellular, less collagenous Grade II tumor with plump cells and "staghorn" vasculature (**A3**) and a low Ki-67 proliferation index (**B3**); it transformed into a highly mitotic Grade III tumor (**A4 and B4**). All tumors show positive STAT6 immunostaining (**C1**, **C2**, **C3**, **and C4**). HE = H & E; Ki67 = Ki-67 labeling index. Figure is available in color online only.

transform into MHPC, however, is a decisive argument for their common identity and tumor initiating cells.

From a clinical point of view, taking into account that initially benign MSFT/HPC may transform into malignant tumors after years of follow-up gives a different perspective on the follow-up and the treatment of patients.

Whether radiotherapy could induce or accelerate malignant progression cannot be established because, in our series, 3 patients had tumors with histological progression without being irradiated before recurrence.

In our series, malignant progressions were diagnosed 3–13 years after the first surgery. As a comparison, in meningiomas, the period of time that elapses to malignant progression ranges from 8 months to 26 years.[1] Longer

follow-up of patients with MSFT/HPC would probably reveal new recurrences and histological progression.

However, unlike meningiomas, MSFT/HPC grading is not yet clearly linked with tumor aggressiveness and prognosis. Some studies have shown that the grade is negatively correlated with progression-free and overall survival,[21] but most attempts to link grading or mitosis count to the onset of local recurrences or somatic metastases were unsuccessful.[2,5,10,11,13]

From a genetic point of view, MSFTs/HPCs, like extracranial solitary fibrous tumors (SFTs), can harbor 2 types of *NAB2-STAT6* fusion gene, either almost entirely conserving *STAT6* (for instance, *NAB2*ex4-*STAT6*ex2), or truncating it and lacking its DNA-binding site (for instance, *NAB2*ex6-*STAT6*ex17).[2] *NAB2*ex6-*STAT6*ex17 and *NAB2*ex6-*STAT6*ex18 are overrepresented in meningeal tumors compared with extracranial tumors and account for up to 70% of *NAB2-STAT6* fusion genes in this location. Otherwise, reports have identified the fusion gene type in 70% of tumors and have shown that they can harbor exon6-exon3, exon4-exon3, exon2-exon2, exon4-exon2 fusions, and others.[7]

It has been shown in small series that tumors with full *STAT6* tend to show an SFT (solitary fibrous tumor) pattern, whereas those lacking a *STAT6* DNA-binding site are more likely to exhibit a malignant phenotype.[20] Even if they are associated with grading, the types of fusion variants are not associated with prognosis, recurrence-free survival, or overall survival.[2,12,20]

Malignant progression may be just one of several mechanisms provoking recurrence and metastasis. There is a strong tendency for Grade III tumors to produce more metastases and a shorter overall survival and recurrence-free interval in some studies (for example, overall survival of 256 months vs 114 months and recurrence-free interval of 95 months vs 59 months for Grade III vs lower-grade tumors, respectively[10]). These results are not always reproducible, especially with respect to metastases,[5] where data are highly uncertain because patients are not systematically examined and only symptomatic metastases are diagnosed. Still, our series seems to confirm this tendency, with a 37% rate of recurrence, with 83% of the recurrent lesions being Grade III at the time of recurrence and a 10% rate of extracranial metastases (occurring in 4 patients with Grade III tumors and 1 with a Grade II tumor). Whether low-grade tumors are more efficiently treated and are less prone to recur after treatment is also unclear, due to the rarity of the disease and the great variability of proposed therapies.[22]

Whether Grade III MSFTs/HPCs are spontaneously aggressive tumors or whether they all progress from lower grades is unclear. In a study of malignant progression in meningioma, 14% to 29% of malignant tumors were first diagnosed at a lower grade,[1] which can be compared with 16% in our MSFT/HPC series. It is also unclear whether Grade I tumors directly become Grade III or if they become Grade II before becoming malignant. Our observations suggest that Grade I and Grade II tumors both transform into malignant Grade III, as no tumor in our series transformed from benign Grade I to benign Grade II. There is no argument for thinking that a particular fusion gene is associated with malignant progression, and some—probably molecular—associated events may be responsible. Some genetic alterations have been identified in Grade III MSFTs/HPCs, such as homozygous deletions of the *CDKN2/p16* gene[14] or *TERT* promoter mutations,[8] and could play a major role in the mechanisms of progression.

Conclusions

Low-grade MSFTs/HPCs can transform into higher-grade tumors. This is a decisive argument in favor of the common identity of MSFT and MHPC. The causality between grading and prognosis is not straightforward, but high-grade MSFTs/HPCs tend to recur more often and shorten overall survival. Malignant progression could be one mechanism explaining some recurrences or metastases, justifying patient information and long-term follow-up even for Grade I tumors. Documenting cases of progression exhaustively is the next step toward molecular investigation through whole-exome sequencing to identify the mechanisms of histological progression and useful immunohistological markers.

Acknowledgments

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kalamarides, Apra. Acquisition of data: Apra, Mokhtari, Peyre. Analysis and interpretation of data: Kalamarides, Apra, Mokhtari. Drafting the article: Apra. Critically revising the article: Kalamarides, Mokhtari. Reviewed submitted version of manuscript: Kalamarides, Apra, Mokhtari, Cornu. Approved the final version of the manuscript on behalf of all authors: Kalamarides. Study supervision: Kalamarides.

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