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Case Report

New Perspectives in the Treatment of Inflammatory Myofibroblastic Tumor with ALK Translocation: Case Report

Johana Benedetti Pedroza Irene Carrasco García Gala Martínez Bernal
Isabel Miras Rodriguez

Medical Oncology Department, Virgen del Rocio University Hospital, Seville, Spain

Keywords
Inflammatory myofibroblastic tumor · Alectinib · ALK inhibitor · Head and neck

Abstract
Introduction: Inflammatory myofibroblastic tumor (IMT) is a rare entity, classified within soft tissue sarcomas. It is an intermediate malignancy tumor, which seldom presents as metastatic disease. The treatment of choice is surgery, except in cases where surgery is not possible due to localization or if it presents with metastatic disease. Approximately 50% of IMTs will exhibit ALK translocation, providing a therapeutic target for these patients. ***Case Presentation:*** A case is presented of a patient with metastatic IMT in complete response to treatment with alectinib, maintained for over 4 years. ***Conclusion:*** This case showed a long time complete response in patient with IMT treated with alectinib.

Introduction

Inflammatory myofibroblastic tumor (IMT) is a mesenchymal tumor of unknown cause and pathogenesis. It occurs in fewer than 1% in 1 million people, according to the 2020 World Health Organization classification; it usually affects young people, children, and adolescents, but it can appear in any age range [1–4]. The lungs, abdomen, head and neck, and retroperitoneum are most commonly affected sites by this neoplasm; however, it can affect other locations of the body [5, 6].

IMT generally shows a benign behavior and surgical resection is usually the standard of treatment in these cases, with a favorable prognosis. On some occasions, up to 30% it may be

Correspondence to:
Irene Carrasco García, irenecg1990@gmail.com

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associated with an inflammatory syndrome characterized by general discomfort, fever, night sweats, weight loss, and pain at the site of the tumor and analytical alterations can be observed such as thrombocytosis and polyclonal hypergammaglobulinemia [6, 7]. However, when the disease presents local recurrence or invasive presentation, the risk of developing metastasis is around 5%, resulting in a more limited prognosis and in some cases, leading to death [8]. IMTs rarely affect the head and neck region. It accounts for 5% of all IMTs and 14–18% of all extrapulmonary IMTs [9–11]. In IMTs located in the head and neck, the orbit is the most frequent site of appearance, and among nasal IMTs, the maxillary sinus seems to be the most common site [9, 10, 12].

Approximately 50% of IMTs will exhibit ALK rearrangement, with overexpression of the transmembrane receptor (ALK-positive). Chromosomal rearrangement involving the ALK locus in 2p23 results in fusion of the 3′ kinase portion of ALK to the 5′ portion of a partner gene; being ALK-positive may be associated with a more favorable prognosis and a therapeutic target for these patients. Other less frequent rearrangements have also been described: ROS1, RET, and NTRK3 [1, 13–15].

We describe the case of a patient with recurrent IMT and translocated ALK who achieved a complete response to date after treatment with alectinib. Alectinib is a potent and highly selective second-generation tyrosine kinase inhibitor of ALK and RET. To our knowledge this is the first case reported in Spain treated with a second generation ALK inhibitor.

Case Report

A 62-year-old woman, who in January 2018 presented with symptoms of general malaise, fever, loss of 4 kg in 1 month and anemia in the transfusion range. Complementary studies were initiated observing a mass of 58 mm located in the lower lobe of the right lung.

Fibrobronchoscopy was performed without conclusive findings. After assessing the case in the tumor board, it was decided to propose a lobectomy, with anatomopathological diagnosis of IMT, fibrohistocytic variant. After surgery, the patient began follow-up.

In June 2018, the patient presented a new lesion located at the level of the upper right incisor, requiring its extraction. However, a few months later, the lesión showed new growth that required re-intervention, confirming IMT relapse, 4 in the last 6 months with pathological anatomy compatible with recurrence of IMT. In February 2019, patient presented new growth of the lesion (Fig. 1.) accompanied by facial pain and limitation for oral intake, the case was sent to a reference center for soft tissue tumors (Virgen del Rocio University Hospital), an image reevaluation was performed (Fig. 2–4), observing a local relapse measuring 22 × 17 mm in the axial plane, Additionally, recurrence was observed at multiple levels, with nodules noted in contact with the nasal spine measuring 8 mm, and multiple nodules in more cranial planes extending to the base of the nasal vestibule. The tumor specimen was reviewed at the reference center, confirming the IMT diagnosis with sarcomatoid areas, neoplasm composed of spindle cells and myofibroblastic cells arranged in a fascicular pattern, there was dense inflammatory infiltrate rich in plasma cells, histiocytes, lymphocytes, and few eosinophils. The spindle cells were soft with variably prominent nucleoli with strong ALK expression, increases the expression of FLI1, and decreases that of CD10 and TLE1 (Table 1).

Considering the recurrence, it was considered that surgical intervention was not possible and systemic treatment was considered. Due to the tumor harbored ALK translocation it was decided in April 2019 to initiate targeted therapy with alectinib at dose of 600 mg per day, resembling, the treatment protocol in ALK-positive lung cancer. A complete response was observed according to RECIST 1.1 criteria in the first reevaluation, which has been maintained to date (Fig. 1b), with good treatment tolerance and no notable acute toxicities, until June

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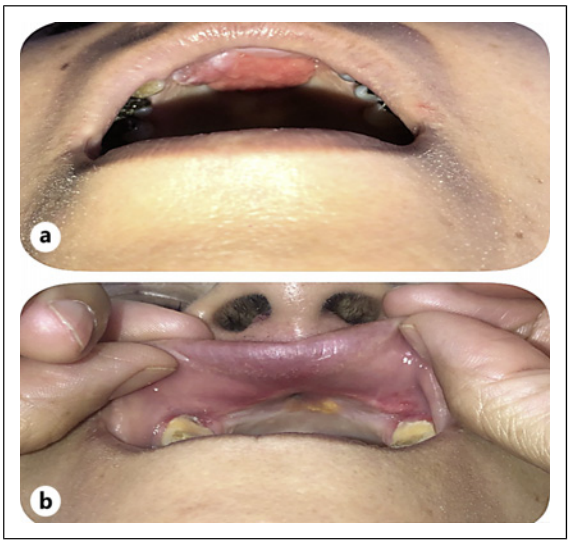

Fig. 1. a Clinical picture: lesion at the level of the upper right incisor compatible with IMT. **b** Clinical picture: complete response after starting treatment with alectinib.

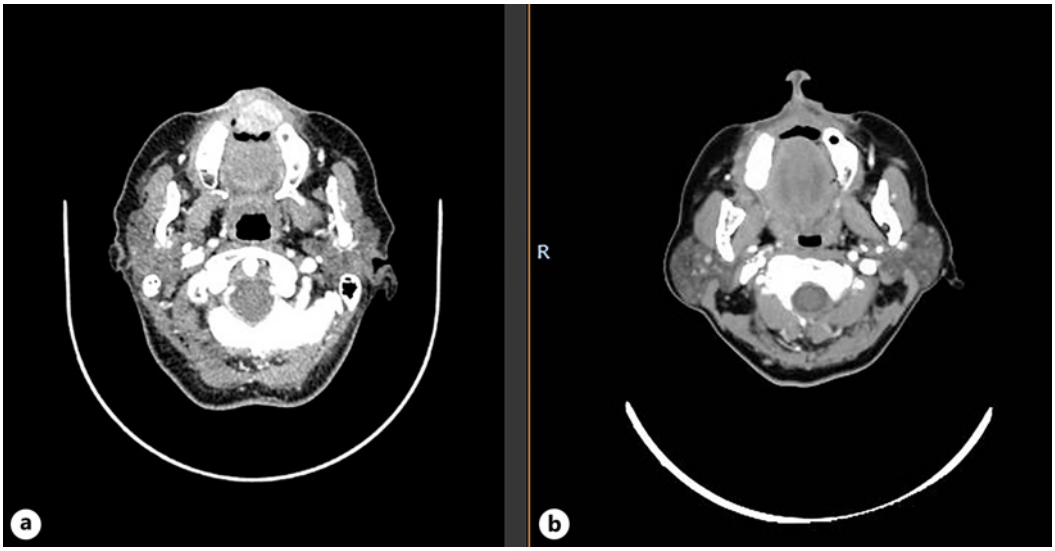

Fig. 2. a Computed axial tomography image showing contrast-enhancing nodular lesion that partially occupies the upper vestibule, measuring 22 mm × 17 mm in diameter. January 2018. **b** Computed axial tomography image showing complete radiological response according to RECIST 1.1 criteria. August 2018.

2022 at this moment the patient presented G2-3 xeroderma, in this context one dose reduction was performed to 450 mg per day with very good tolerance to date. Last image review was performed, maintaining a complete response (Fig. 5).

Discussion

We present a case of a 62-year-old woman with IMT located in the lung and treated with surgery, achieving a complete resection with a lower lobectomy. However, the patient experienced a metastatic relapse at the level of the incisor. As observed in our

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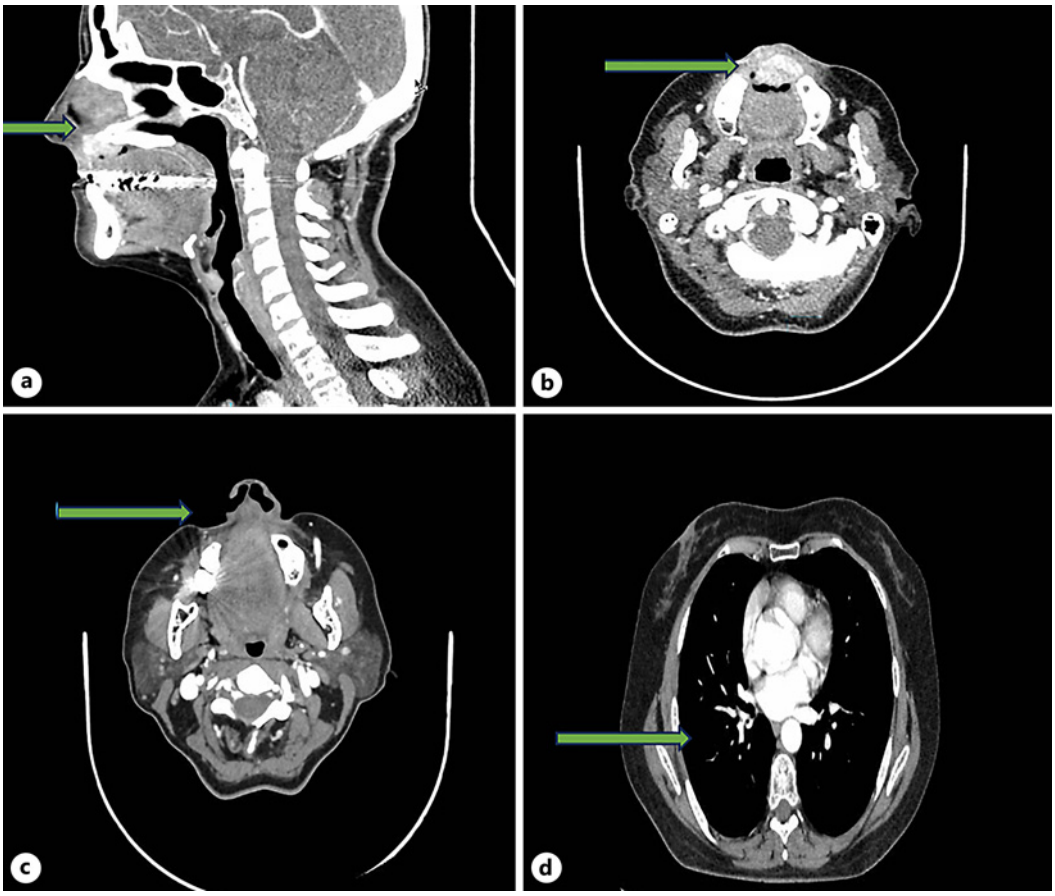

Fig. 3. Images of the evolution of target lesion response during treatment. **a**, **b** Focal nodular lesion measuring 12 × 13 mm with contrast hyperenhancement, partially occupying the upper vestibule, well defined, slightly heterogeneous. **c**, **d** CT scan after 5 months of treatment with alectinib in pathological complete response according to RECIST 1.1 criteria.

case, the recurrence occurred in a different organ than the initial diagnosis and with high cytoplastic expression of ALK. In this context, an excellent response was achieved with alectinib.

IMT was considered a benign tumor with the capacity for local destruction; however, currently cases with metastatic potential have been described [16, 17].

The IMT occurs in soft tissue and viscera and can appear in any location, with no preference for age or gender. It occurs primarily in the lungs but has been described in other extra-pulmonary sites [2]. Between 14 and 18% can be located in the head and neck as is the case of our patient [9, 10, 18].

IMT is characterized by a myofibrotic background with a significant inflammatory infiltrate and may be the result of chromosomal alterations such as the translocation and overexpression of the ALK kinase, which is often assessed using immunohistochemical studies [19]. The ALK gene (chromosome band 2p23) has been implicated in the pathogenesis of IMT, supporting the neoplastic origin of the tumor. Approximately 50% of all IMTs have been associated with ALK positivity [20, 21]. However, the majority of described cases of oral IMT do not present ALK translocation, leading to less aggressive behavior and lower potential to metastasize. This is why ALK-positive IMTs has been proposed as a different entity.

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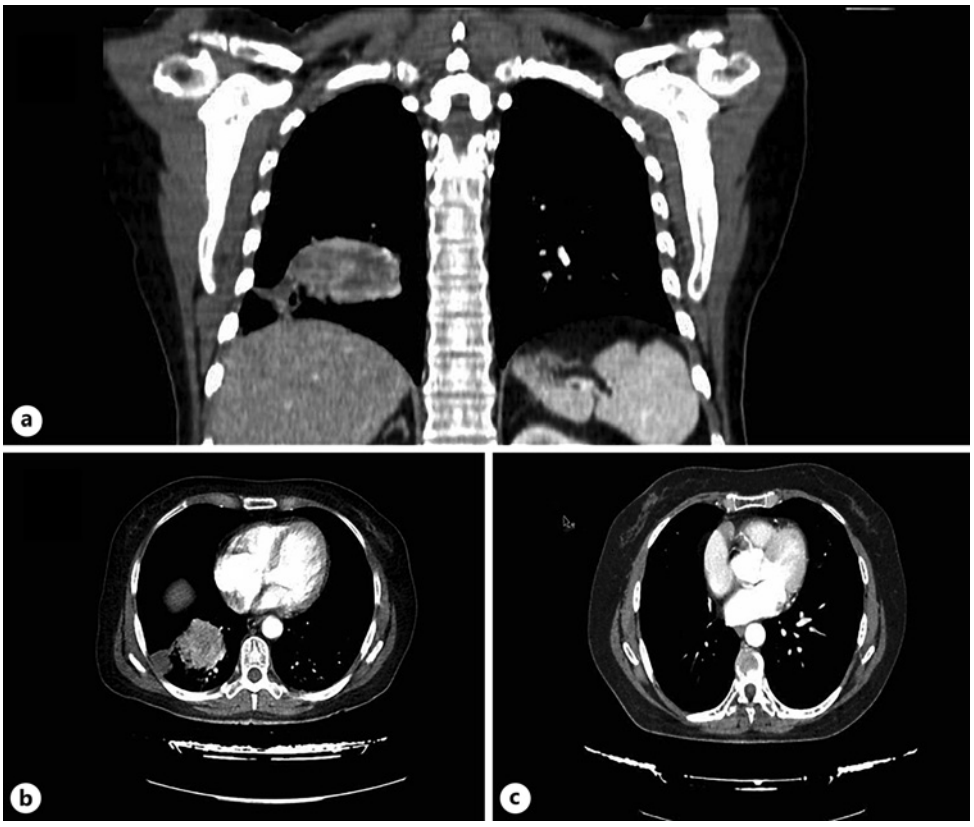

Fig. 4. Evolution of the lung metastasis. **a**, **b** January 2018, image of mass approximately 56 mm in maximum diameter, located in the right lower lobe. **c** August 2019, control CT scan after lobectomy.

Table 1. Pathological characteristics of the case

Feature	Markers/indicators	Expression
Vascular richness	CD34, AML	Positive (high vascular density)
Proliferating cells	Clear nuclei, visible nucleoli	–
Markers expressed	CD10, FLI1, TLE, ALK	CD10, FLI1, TLE (irregular); ALK (intense)
Proliferation index	–	High (35% in some areas)
Markers not expressed	Pancytokeratin, desmin, S-100, HMB45, Melan-A, STAT6, calretinin, CD117, BCL-2, CD99	Negative

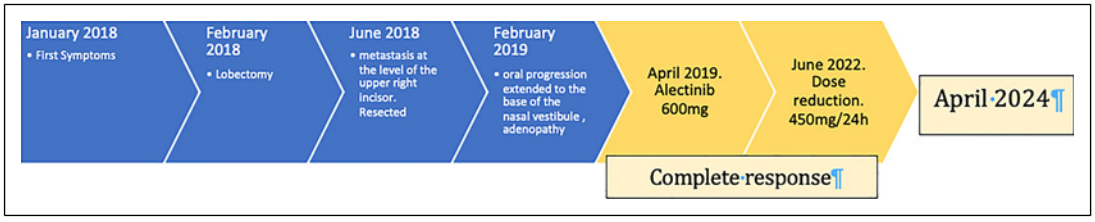

Fig. 5. Timeline. Disease evolution.

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Table 2. These summaries provide an overview of case reports regarding the use of alectinib in treating IMTs

MID	Title	Authors	Journal	Year	Summary
36754839	Alectinib for the treatment of ALK-positive inflammatory myofibroblastic tumor: A case report and literature review	Wang [26]	Medicine (Baltimore)	2023	This case report discusses the efficacy of alectinib in treating a patient with ALK-positive IMT. The patient showed a significant clinical response, suggesting that alectinib could be a viable treatment option for such cases. The report also reviews relevant literature to support these findings
36032811	Targeted therapy with alectinib in patients with ALK-positive inflammatory myofibroblastic tumor: A multicenter retrospective study	Kim [27]	Cancer Chemotherapy and Pharmacology	2022	This multicenter retrospective study evaluates the effectiveness of alectinib in patients with ALK-positive IMTs. The study found that alectinib is effective and well-tolerated, providing a new therapeutic option for patients with this rare tumor type. Results indicated improved progression-free survival and manageable side effects
36635892	Efficacy of alectinib in ALK-positive inflammatory myofibroblastic tumors: A case series and review of the literature	Jones [28]	BMC Cancer	2023	This article presents a case series of patients with ALK-positive IMTs treated with alectinib. All patients experienced significant tumor regression or stabilization, highlighting the potential of alectinib as a targeted therapy. The study also reviews existing literature, reinforcing the therapeutic promise of alectinib for these patients
30790150	Response to alectinib in ALK-positive inflammatory myofibroblastic tumor of the lung: A case report	Matsui [29]	Case Reports in Oncology	2019	This case report details the response of a lung IMT patient to alectinib. The patient showed marked tumor reduction and symptom improvement, indicating that alectinib is effective in treating ALK-positive IMTs in the lung. The report suggests alectinib as a promising therapeutic option for similar cases

(Continued on following page)

Table 2 (continued)

MID	Title	Authors	Journal	Year	Summary
28977547	Alectinib in ALK-rearranged inflammatory myofibroblastic tumor of the lung: Case report and review of the literature	Imai [30]	Lung Cancer	2017	The case report discusses the treatment of an ALK-rearranged IMT in the lung with alectinib. The patient experienced significant clinical improvement, supporting the use of alectinib for treating ALK-rearranged IMTs. The article includes a literature review to provide context and support for the findings
29439172	Alectinib for ALK-rearranged inflammatory myofibroblastic tumors: Two case reports and literature review	Nakamura [31]	Oncology Letters	2018	This article presents 2 case reports of patients with ALK-rearranged IMTs treated with alectinib. Both patients showed significant responses, with tumor regression and symptom relief. The article reviews the literature on ALK inhibitors in IMTs, supporting the potential role of alectinib in treating this rare and challenging condition

In our case, it is suspected that it could be ALK positive due to the multiple recurrences seen. Cytogenetic and molecular studies point to the possibility that some subsets of IMTs are in fact true monoclonal neoplasms and are also invasive and locally recurrent. It is described as a possibility that, instead of discussing a metastatic situation, it could be a multicentric tumor rather than true metastasis.

Possible causes have been described that can trigger the development of an inflammatory process with the release of cytokines and interleukin-1 (IL-1) in response to an insult, causing proliferation of fibroblasts, permeable endothelium, procoagulant and extravasation of polymorphs with cellular infiltrate in the extracellular spaces [4]. Some authors assume an association with a trauma, infection (infections of HHV8 and EBV) with overexpression of IL-6, and cyclin D1 have been reported [22, 23]. Clinically, the symptoms will depend on the location of the tumor, extrapulmonary IMTs can be accompanied by constitutional symptoms, such as fever, anemia, and weight loss, as was the case with our patient [24].

The pathological diagnosis can be a challenge due to the inflammatory, plasmacytic, histiocytic component, and the wide morphological spectrum. Therefore, some autoimmune diseases can simulate an inflammatory pseudotumor, such as lupus erythematosus and rheumatoid arthritis [25].

The differential diagnosis of IMT comprises low grade myofibroblastic sarcomas as well as a long list of benign, reactive, or neoplastic spindle cell lesions, such as leiomyoma, solitary fibrous tumor, spindle cell carcinoma, nodular fasciitis, and peripheral nerve sheet tumor. Most have a benign behavior with low recurrence, which is why radical surgery is the treatment of choice. In the past, chemotherapy and radiation therapy were used but were

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found to be ineffective [19]. The future treatment lies in targeted therapy that will inhibit the growth of the tumor.

The use of targeted therapy in those with ALK translocation is documented in the literature, with guidelines recommending the use of crizotinib. In this clinical case, we highlight the use of second-generation targeted therapies, achieving in our case a sustained complete response which has been maintained beyond 24 months with minimal side effects (Table 2).

Conclusion

IMT is a rare tumor, of unknown cause and often difficult to diagnose, so it should be considered in a patient with a persistent inflammatory lesion in the oral cavity or other location. An adequate morphological and histological diagnosis is important to help us in making therapeutic decisions. The first treatment option depending on the size and location continues to be surgery; however, for those patients who have overexpression of ALK, we have target treatments that are well tolerated and with high response rates, maintaining adequate control of the disease, providing quality of life for our patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539739).

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. The authors state that they have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Johana Benedetti Pedroza has collected research funding for clinical studies (institutional) from PharmaMar, Eli Lilly and Company, AROG, Bayer, Eisai, Lixte, Karyopharm, Deciphera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daichii-Sankyo. Irene Carrasco García has received personal fees for advisory board, consulting, and travel expenses from Pharmamar. She has also gotten research funding for clinical studies (institutional) from PharmaMar, Eli Lilly and Company, AROG, Bayer, Eisai, Lixte, Karyopharm, Deci-phera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daichii-Sankyo. Gala Martínez Bernal has obtained research funding for clinical studies (institutional) from PharmaMar, Eli Lilly and Company, AROG, Bayer, Eisai, Lixte, Karyopharm, Deci-phera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daichii-Sankyo. Lastly, Isabel Miras Rodriguez has obtained research funding for clinical studies (institutional) from PharmaMar, Eli Lilly and Company, AROG, Bayer, Eisai, Lixte, Karyopharm, Deci-phera, GlaxoSmithKline, Novartis, Blueprint, Nektar, Forma, Amgen, and Daichii-Sankyo.

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Author Contributions

J.B.P., I.C.G., G.M.B., and I.M.R. made substantial contributions to the conception or design of the work and acquisition, analysis and interpretation of the data. All authors also contributed to the drafting and critical review of the content, approved the final version to be published, and are accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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