

CASE REPORT

Small cell neuroendocrine carcinoma: A rare second primary malignancy after treatment of nasopharyngeal carcinoma

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ABSTRACT

Small cell neuroendocrine carcinoma (SCNEC) of the nasopharynx and nasal cavity is a rare condition. It is an aggressive malignancy with a high recurrence rate. Despite its rarity in the sinonasal region, it may occur as a second primary malignancy. Patients with cancer of the head and neck region are more prone to develop a second primary tumor due to the field cancerization phenomenon, and a higher incidence is seen in those who have previously received radiation therapy. A detailed clinical and histopathological examination is pivotal to diagnose SCNEC as a second primary malignancy. We wish to highlight such a peculiar case from our center.

KEYWORDS: neuroendocrine carcinoma, nasopharyngeal carcinoma, second primary malignancy, small cell carcinoma.

INTRODUCTION

Patients who have successfully received treatment with radiation therapy have a risk of developing a new malignancy later on¹. An example of such an entity is the development of small cell neuroendocrine carcinoma (SCNEC) after successful treatment of nasopharyngeal carcinoma (NPC) by radiation therapy. Extrapulmonary small cell carcinomas are rare, accounting for only 0.1-0.4% of all malignancies and 2.5-4% of all small cell carcinomas². Such a tumor occurring in the sinonasal tract is very uncommon. However, when such a tumor occurs as a second primary malignancy in the nasopharynx, it represents an even rarer situation³.

CASE REPORT

A 68-year-old female presented with blood-stained nasal discharge for two weeks prior to consultation. She had T1N3M0 non-keratinizing

squamous cell carcinoma of the nasopharynx 4 years before (confirmatory biopsy was taken from the right fossa of Rosenmüller). She was successfully treated with concurrent chemo- and radio-therapy (CCRT). Radiation therapy was divided into two phases. In the first phase, she received a total dose of 40 Gray (Gy) in 20 fractions to the neck and fasciocervical region. In the second phase, she received a total of 30 Gy in 15 fractions to the fasciocervical region, then 20 Gy in 10 fractions to the anterior neck and finally 26 Gy in 13 fractions to the right and left side of the posterior neck. After the radiation therapy, she underwent 5 cycles of chemotherapy (cisplatin) on a weekly basis. The 6th cycle of cisplatin was withheld due to leukopenia. Upon completion of treatment, she was monitored closely and was in remission. During her 4th year of routine surveillance, a rigid nasal endoscopy revealed a suspicious mass over the posterior free margin of the nasal septum (right side) (Figure 1).

Subsequently, a Positron Emission Tomography

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Received for publication: May 20, 2018 / Accepted: June 12, 2018

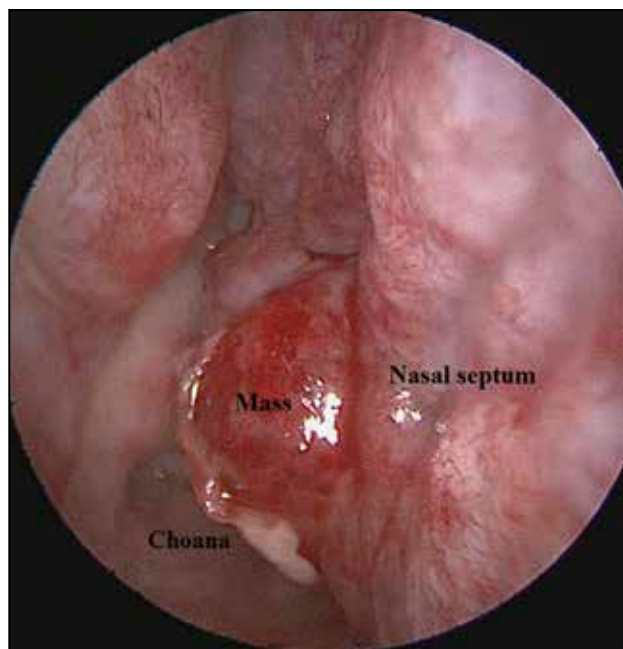


Figure 1 Endoscopic view of the posterior free margin of the nasal septum (right side).

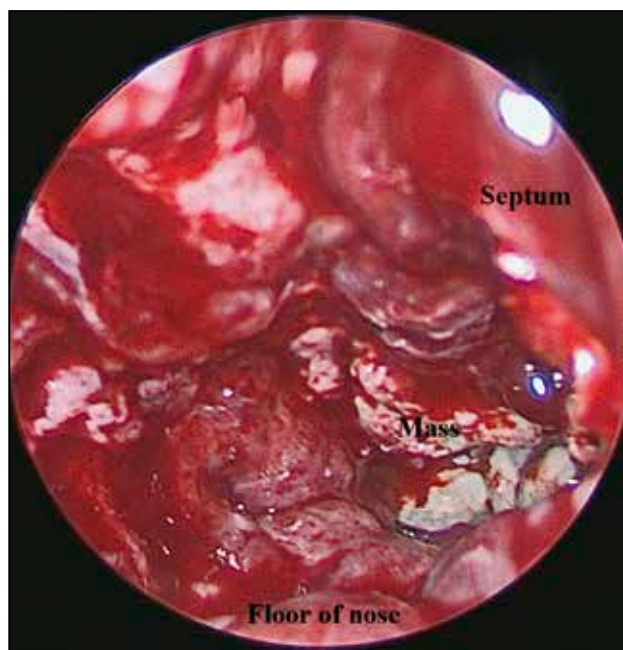


Figure 3 Endoscopic view of the nasopharynx showing a yellowish-white mass obscuring the entire nasopharynx.

– computed tomography (PET-CT) scan was done. This scan confirmed fluorodeoxyglucose (^{18}F -FDG) avid malignancy of the soft tissue mass over the posterior end of the nasal septum's right side with a Standardized Uptake Value (SUV) of 6.2. There was also a bulky posterior nasopharynx (left side) with a SUV of 5.2 (Figure 2).

Otherwise, the nasal cavity and the rest of the

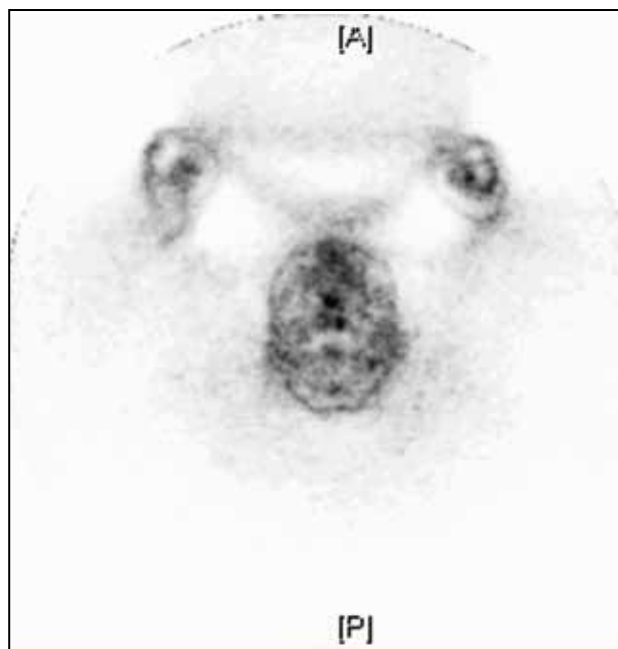


Figure 2 PET-CT scan showing avid malignancy of the soft tissue mass over the posterior end of the nasal septum's right side with Standardized Uptake Value (SUV) of 6.2, as well as a bulky posterior nasopharynx (left side) with a SUV of 5.2.

body were free of disease.

A wide local excision of the nasal mass along with posterior septectomy was done successfully under general anaesthesia. The histologic examination confirmed a diagnosis of neuroendocrine carcinoma. She was scheduled for adjuvant Intensity Modulated Radiotherapy; however, she was undecided for the treatment. She was followed up closely with no evidence of obvious local residue or recurrence of the disease.

In the 4th post-operative month she complained of reduced hearing in her right ear and a severe throbbing headache. A detailed clinical examination revealed a right-sided middle ear effusion with no other anomalies. The rigid nasal endoscopy showed that the nasal cavity mucosa on both sides was severely congested. There was a yellowish-white mass occluding the entire nasopharynx (Figure 3).

Biopsies of the mass taken under general anaesthesia confirmed high-grade SCNEC. The microscopic examination of the lesion using haematoxylin and eosin (H&E) stain showed multiple fragments of tumor tissue focally covered by respiratory epithelium. The underlying stroma showed malignant cells infiltrating in trabeculae, irregular nests and islands accompanied by prominent vascular channels and a moderate lymphoplasmacytic cell infiltrate (Figure 4). The cells displayed round to oval nuclei with fine stippled chromatin pattern and indistinct scanty cyto-

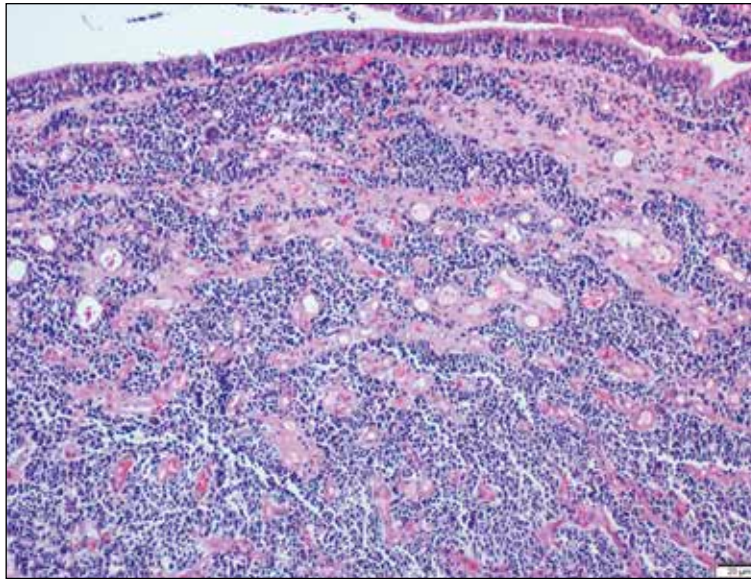


Figure 4 Malignant cells arranged in trabeculae, irregular nests and islands accompanied by prominent vascular channels. The overlying respiratory epithelium was unremarkable (Hematoxylin and eosin stain, original magnification x 100).

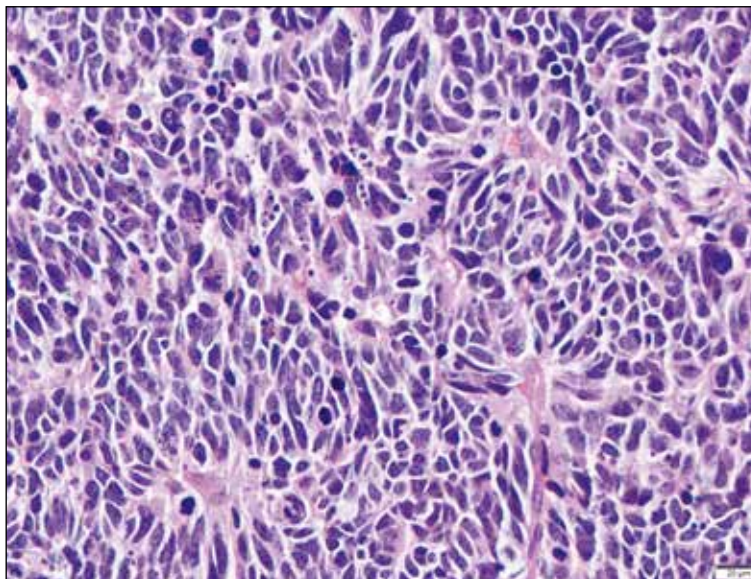


Figure 5 The malignant cells displayed round to oval nuclei with fine stippled chromatin pattern and indistinct scanty cytoplasm. Mitotic figures and apoptotic bodies were frequently seen. Occasional nuclear moulding was also noted (Hematoxylin and eosin stain, original magnification x 400).

plasm. Mitotic figures and apoptotic bodies were frequently seen. Occasional nuclear moulding and tumor necrosis were also noted (Figure 5). The cells were immunoreactive for CKAE1/AE3 (diffuse, cytoplasmic & perinuclear dot-like positivity), Synaptophysin (diffuse), and Chromogranin A (in one focus). The Ki-67 proliferative index was 99%. Other markers to rule out differential diagnosis of sinonasal tract tumors were negative

(S100, LCA, CD99, SMA and desmin). There was no squamous or glandular differentiation observed. The overlying respiratory and squamous epithelium was unremarkable. Based on the histological and immunohistochemical profile, a diagnosis of high-grade SCNEC was made.

Staging computed tomography (CT) scan revealed liver metastasis and she succumbed to her disease shortly thereafter.

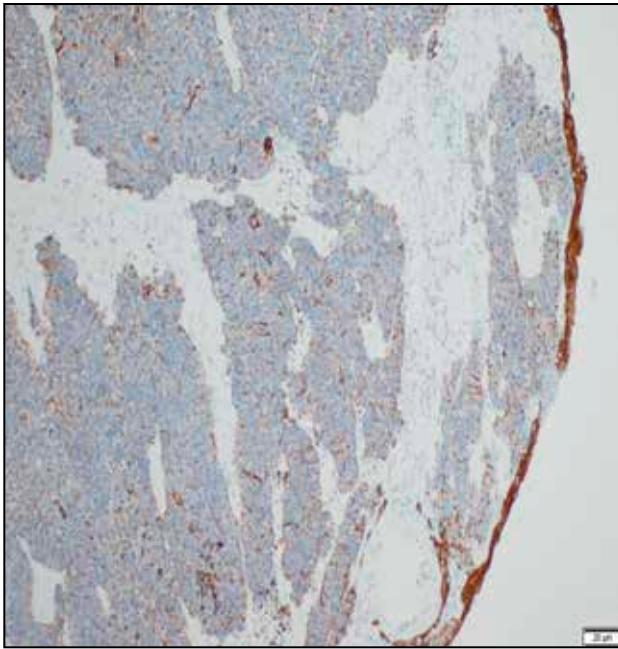


Figure 6 The malignant cells were immunoreactive for CKAE1/AE3 (Immunohistochemical stain, original magnification x 100).

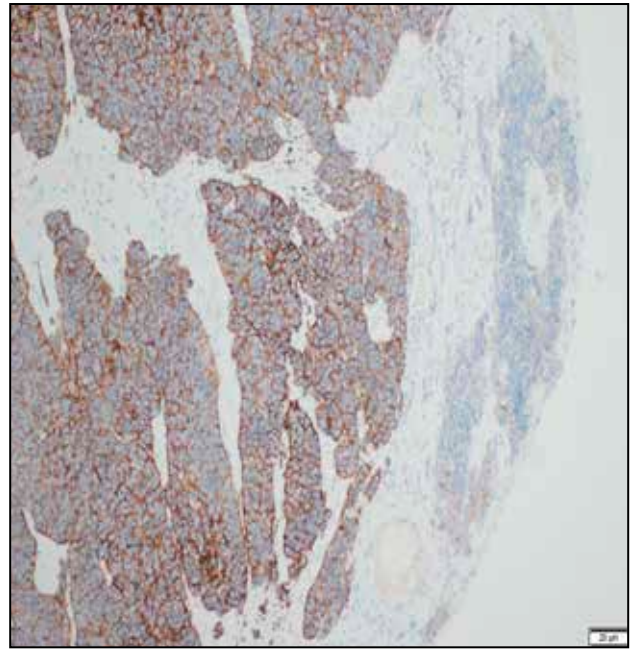


Figure 7 The malignant cells were immunoreactive for Synaptophysin (Immunohistochemical stain, original magnification x 100).

DISCUSSIONS

Sinonasal malignancies make up less than 5% of all head and neck cancers⁴. Neoplasms of various cellular origin including epithelial (most common)^{5,6}, mesenchymal and neuroectodermal differentiation may arise in the sinonasal tract. Malignancies with neuroendocrine differentiation are rare in the sinonasal tract⁶. A tumor of such differentiation is rarely seen in the head and neck region³, the lungs being the commonest primary site^{7,8}. Neuroendocrine tumors may arise in sites that typically do not contain neuroendocrine cells. Such sites do not imply embryologic derivation from neuroectoderm. It only reflects a shared phenotype characterized by expression of multiple genes encoding both the neuronal and the endocrine feature⁹.

Extra pulmonary SCNECs are rare, accounting for only 0.1 - 0.4% of all malignancies² and 2.5 - 5% of all SCNECs⁷, with the larynx being the commonest extrapulmonary site involved⁸. The incidence of a second primary malignancy developing in patients who were previously treated with radiotherapy for nasopharyngeal carcinoma was reported at 0.7%, with onset occurring 5-18 years after the treatment⁸. Much of the cellular and molecular evidence support the field metastasis theory. SCNEC is a high-grade poorly differentiated neuroendocrine tumor⁷ which is known for its cellular aggressiveness and poor prognosis³. SCNEC is also known as poorly dif-

ferentiated neuroendocrine carcinoma. Barnard was the first to describe it in 1926, using the term oat cell sarcoma^{3,8}. Silva et al. went on to describe sinonasal neuroendocrine carcinoma in 1982¹⁰. Reports show that the median age of presentation of patients with sinonasal neuroendocrine carcinoma ranges between 50-57 years⁴.

Sinonasal primary neuroendocrine tumors are represented by a spectrum of four major histologic phenotypes: esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinoma and small cell undifferentiated carcinoma¹¹. However, due to the rarity of this disease, with no definite classification, the World Health Organization (WHO) addressed this issue in 2005 and classified it as: i) typical carcinoid, ii) atypical carcinoid, iii) small cell carcinoma neuroendocrine type, iv) sinonasal neuroendocrine carcinoma not otherwise specified and v) paraganglioma⁴. SNUC and ENB were not included in the WHO classification.

As evidenced in our case, SCNEC of the nasopharynx may present with a yellowish-white mass⁵. Our patient developed SCNEC as a second primary malignancy 4 years after successful completion of CCRT treatment. To establish a newly diagnosed second primary malignancy in the nasal cavity or nasopharynx, various criteria must be met. Each neoplasm must be geographically disparate with no dysplasia in the intervening mucosa, the possibility of the second primary tumor representing a metas-

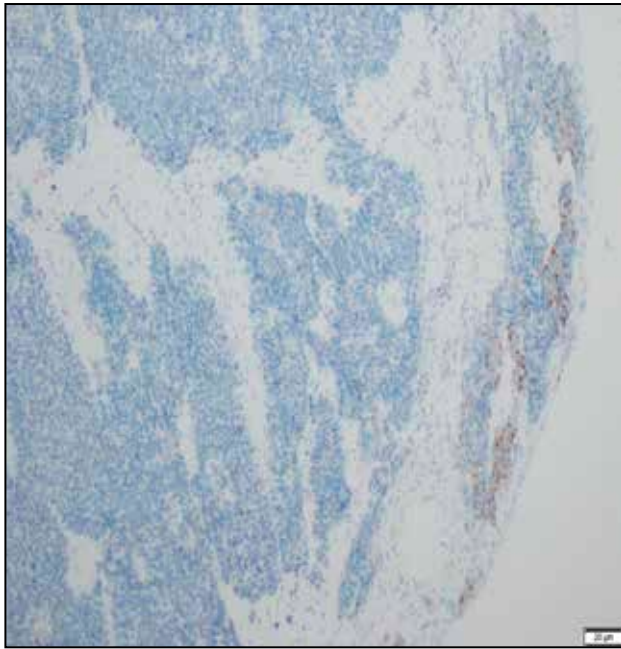


Figure 8 The malignant cells were immunoreactive for Chromogranin A in a focal area (Immunohistochemical stain, original magnification x 100).

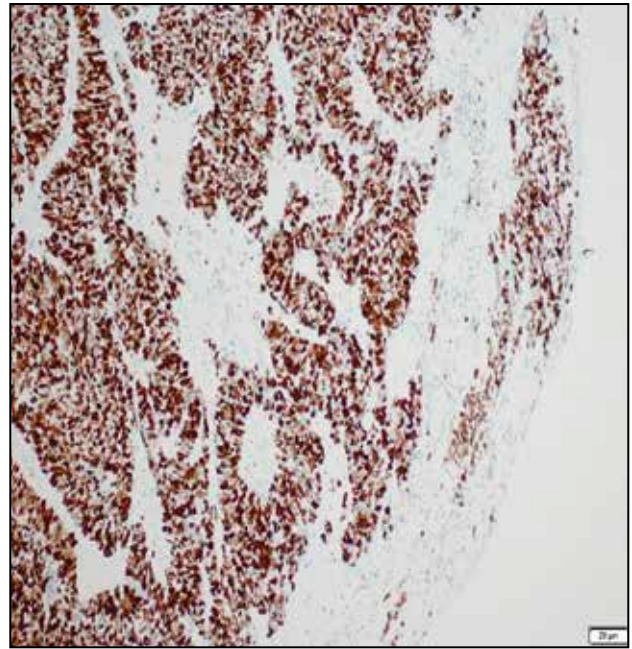


Figure 9 The Ki-67 proliferative index was high, 99% (Immunohistochemical stain, original magnification x 100).

tasis or relapse must be excluded, the second primary malignancy has to be separated from the first by at least 2cm of normal epithelium, or, has to occur at least 3 years after diagnosing the first primary cancer¹. The diagnosis of a second primary malignancy in our case is based on the aforementioned criteria. Firstly, the second tumor occurred 4 years after the treatment of NPC. Secondly, during the patient's entire surveillance period post CCRT, there was no evidence of recurrence. Thirdly, the second tumor was localized in the nasal septum and there was only a minimal involvement of the left side of the nasopharynx (based on the PET-CT scan) and, lastly, the histopathologic evidence showed difference of tumor type from the initial one and this second primary malignancy. The patient subsequently developed local recurrence of disease, despite complete surgical excision with clear margins (R0 resection). This is in keeping with the fact that SCNECs are aggressive tumors with a local recurrence rate of 45%^{3,9}.

Conventional microscopic histopathologic examination alone does not suffice to arrive at the diagnosis of SCNEC. Further immunohistochemical studies help to exclude other sinonasal neoplasms such as lymphoma, ENB, malignant melanoma, and SNUC⁵. Although SCNEC can be quite similar to ENB morphologically and immunohistologically, there are specific features that can be used to differentiate these two mimickers. ENB shows neurofibrillary background, with evi-

dence of Homer Wright pseudorosette formations⁸. Furthermore, ENB shows immunoreactivity for S100 protein in cells located at the periphery of cell nests. Tissue samples from our case were immunoreactive for pan-cytokeratin, Synaptophysin and Chromogranin A (Figure 6, Figure 7 and Figure 8). The Ki-67 proliferative index was 99 % (Figure 9).

SNUC generally is Synaptophysin and Chromogranin negative^{4,5} and ENB is rarely positive for cytokeratin⁶. ENB may be positive for cytokeratin only in the Homer Wright pseudorosette areas⁴. S100, LCA and CD99 stains were all negative in our case, thereby ruling out malignant melanoma, lymphoma and small round blue cell tumors⁵.

Since SCNEC of the nasopharynx is rare, no specific therapeutic guidelines are available. However, therapy is based on evidence regarding the treatment of pulmonary small cell carcinoma³. A multimodality treatment has been recommended. It consists of the combination of chemotherapy (cisplatin based) and radiotherapy, with or without surgery⁸. Unfortunately, in SCNEC it is common to find distant metastasis due to notable haematogenous dissemination to lymph nodes, liver, lungs and bone³ with rates of metastasis as high as 35%^{2,9}. Our patient was found to have liver metastasis when she was diagnosed with recurrence of her disease. Primary nasopharyngeal neuroendocrine carcinoma with liver metastasis carries a poor prognosis and an overall survival of 10 months¹².

CONCLUSIONS

Head and neck cancer patients are at an elevated risk of developing a second primary tumor in the upper aerodigestive tract attributable to the field cancerization phenomenon¹. Diagnosis of neuroendocrine carcinoma of the sinonasal tract is a challenge by itself. Ancillary studies like immunohistochemistry play a crucial role in obtaining its diagnosis⁵. Despite the lack of a consensual therapeutic protocol, the multimodality multidisciplinary team approach is needed to treat SCNEC of the nasopharynx³. Primary SCNEC of the head and neck region carries a poor prognosis with a median overall survival reported at 14.5 months, and a three-year survival rate of 23.7%.

Conflict of interest: The author and all co-authors have no conflict of interest.

Contribution of authors: All authors have equally contributed to this work.

Acknowledgements: This case report was written by Dr. Madhusudhan Krishnamoorthy. All co-authors have read and agreed to the final version of this manuscript, and have equally contributed to its content, as well as the management of the case.

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