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Case report

Collision tumors of the lung: A case report of urothelial carcinoma metastasizing to renal cell carcinoma with heterotopic ossification

Kei Shing Oh [a,*,1], Hisham F. Bahmad [a,1], Christopher A. Febres-Aldana [a], Fernando M. Safdie [b], Vathany Sriganeshan [a,c]

[a] Arkadi M. Rywlin M.D. Department of Pathology and Laboratory Medicine, Mount Sinai Medical Center, Miami Beach, FL, USA
[b] Department of Thoracic and Cardiovascular Surgery, Mount Sinai Medical Center, Miami Beach, FL, USA
[c] Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

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ABSTRACT

Collision tumors are rare entities that consist of at least two or more histologically and ontologically distinct tumor types within the same organ. It is still not well understood how collision tumors form; yet, three main theories have been proposed to explain the pathogenesis, including the "random collision effect," "field cancerization," and "tumor-to-tumor carcinogenesis." Collision tumors have been encountered in various body organs, including the lung. They either consist of a metastasizing tumor colliding with primary cancer or distinct primary or metastatic cancers colliding together. Here, we describe a rare case of collision tumors of the lung that consists of two metastatic carcinomas, namely renal cell carcinoma and urothelial carcinoma of the bladder. We propose that the urothelial carcinoma disseminated into several pre-existing pulmonary metastases of renal cell carcinoma with heterotopic bone formation. The possible mechanisms underlying the development of this peculiar tumor are discussed.

1. Introduction

Collision tumors are rare entities that refer to the concurrent existence of two or more independent histologically distinct tumor types within the same anatomic location [1–3]. They consist of at least two neoplastic cell populations, with different clonal ancestors and genetic background, colliding and expanding into each other. The term "collision tumor" goes back to the mid-1900s [4,5] when common sites of occurrence were described, including the stomach [6,7], lungs [8–10], liver [11,12], and adrenals [13,14] among others [15–18]. The mechanism by which collision tumors form is not fully understood; however, one of the following three theories might explain the pathogenesis and occurrence of this phenomenon: "random collision effect" [19–21], "field cancerization" [21,22], and "tumor-to-tumor carcinogenesis" [1].

The lung is one of the most common recipients of metastatic spreading; thus, several case reports describe collision tumors between either primary lung cancer and metastasizing tumor to the lung [9,10,23,24] or distinct primary lung cancers colliding together [17,25–28]. However, it is infrequent to have a collision tumor that consists of two different non-pulmonary tumors metastasizing to the lung. Nakamura et al. described pulmonary metastases of colon and prostate adenocarcinomas to the same lung lobe but without collision [29]. Herein, we present a case of 79-year-old man with three separate nodules of collision tumors in the right lower lung lobe consisting of two metastatic carcinomas, namely clear cell type renal cell carcinoma (RCC) and high-grade urothelial carcinoma (HGUC) of the bladder. We also discuss the possible mechanisms underlying the development of these collision tumors. This case is presented following the Surgical CAse REports (SCARE) guidelines for reporting case reports.

2. Case presentation

A 79-year-old man, ex-smoker, presented to the urology office for follow up of suspicious computerized tomography (C.T.) scan findings. The patient presented with worsening fatigue for few months. He also reported weakness and shortness of breath with exertion but denied any

* Corresponding author. Anatomical and Clinical Pathology Resident, Arkadi M. Rywlin M.D. Department of Pathology and Laboratory Medicine, Mount Sinai Medical Center, 4300 Alton Rd, Miami Beach, FL, 33140, USA.
E-mail address: KeiShing.Oh@msmc.com (K.S. Oh).
[1] Authors contributed equally to this work as co-first authors.

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cough, fever, or chills. There was no family history of cancer. The patient's medical history included hypertension, hypercholesterolemia, diabetes mellitus, and atrial fibrillation, treated with the following medications: Apixaban, Amlodipine besylate/Benazepril, Atorvastatin, Labetalol, Metformin, Doxazosin, and Glipizide. He had previously undergone partial nephrectomy for RCC. Physical examination revealed a right pleural effusion and abdominal tenderness.

A CT imaging of abdomen and pelvis with contrast revealed an infiltrative 7.5 cm right upper pole renal mass involving the collecting system with renal vein extension (Fig. 1C). There was marked atrophy of the inferior right renal pole with dystrophic calcifications and renal calculi. A 2.4 cm sessile bladder mass involving the left lateral wall, with retroperitoneal and left iliac lymphadenopathy was noted (Fig. 1B). The right middle and lower lobes of the lung showed atelectasis secondary to the right pleural effusion. There was a posterior pleural-based enhancing mass at the right inferior pleural cavity measuring 2.3 cm. Multiple pulmonary nodules were seen in the bilateral lungs, with the largest nodule measuring 1.8 cm (Fig. 1A).

At the emergency department, a thoracentesis was performed, recovering 3.2 L of serosanguinous fluid. Cytology of the pleural fluid showed highly atypical cells suspicious for carcinoma. Cystoscopy with transurethral resection of bladder tumor was performed. Pathologic examination revealed a muscle-invasive HGUC with vascular invasion. The patient was discharge home with outpatient follow-up.

A week later, the patient developed a syncope in the setting of acute kidney injury. A Chest x-ray showed persistent nodular opacities over the right lower and left lower lungs; diffuse congestive changes but increasing effusion and atelectasis at the right lung base. In view of progression of the malignant pleural effusion, the patient underwent robotic right video-assisted thoracoscopy and talc pleurodesis with flexible bronchoscopy. A wedge resection of the superior segment of the right lower lobe was performed. Gross examination revealed three well-circumscribed discrete nodules with a tan-white firm cut surface, measuring 1.5 cm, 0.9 cm, and 0.7 cm, in greatest dimension, respectively. Microscopically, the nodules were composed of two morphologically distinct cellular populations (Fig. 2). The metastatic RCC component, composed of clear cells with prominent nucleoli, was observed at the core and periphery of the nodules showing immunoreactivity to PAX-8 and vimentin. In the nodule core, the RCC was admixed with sheets of metastatic HGUC cells, which stained positive for cytokeratin (CK)-7, CK-20, and GATA binding protein 3. Remarkably, the microvasculature of the RCC harbored foci of circulating HGUC cells. There was stromal and vascular calcification and heterotopic bone formation in the RCC. Thyroid transcription factor-1 (TTF-1) stain was negative in both components, ruling out a primary lung carcinoma component (Fig. 3).

The patient later developed postoperative septic shock with acute acalculous cholecystitis and died after one month.

3. Discussion

The present case disclosed concurrent pulmonary metastases from kidney (RCC) and bladder (HGUC) cancers. The occurrence of metastatic non-pulmonary carcinoma with primary lung cancer at the same location in the lung has been reported [9,10,23,24]; however, simultaneous pulmonary metastases from kidney and bladder cancers are uncommon. A collision tumor refers to the coexistence of two or more tumors harboring different morphology, and clonal, and organ-specific origins within the same location but with none or minimal histological admixture [21]. The term "collision tumor" should not be confused with the term "mixed tumor," which encompasses histological admixture of different tumoral cell types – thought to have a common cell of origin, e.g. myoepithelial carcinoma and fibroadenoma – in the same organ [30,31]. An entity that is also close to the two aforementioned terms and should be differentiated from them is "composite or combined tumor," where the tumor is composed of cell populations with different histopathology and clonal origins, but they are originated in the same primary organ, such as thyroglobulin positive papillary carcinoma cells and calcitonin-positive medullary carcinoma cells [32].

Several theories have been postulated to explain the formation of collision tumors (Fig. 4). One model known as the "random collision effect" theory supports the notion that such tumors develop coincidentally by chance due to accidental meeting of two or more coexisting malignancies in the same organ [19–21]. Another theory considers that

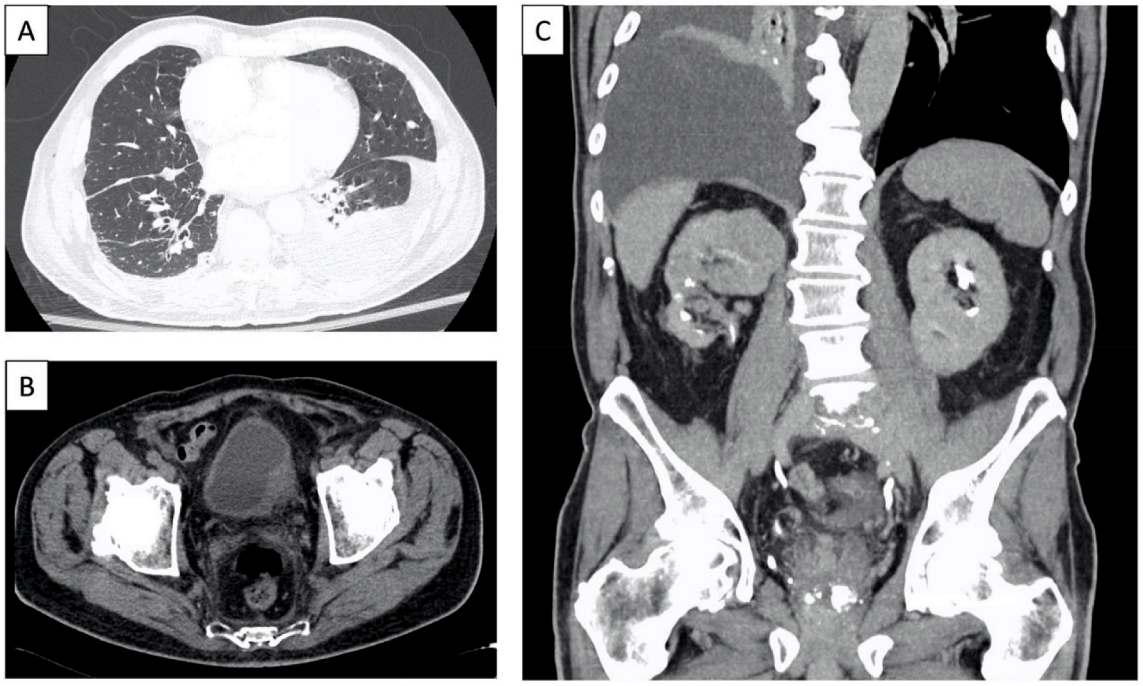

Fig. 1. CT scan images of the (A) lung showing multiple metastatic nodules, (B) bladder mass in the left lateral wall, and (C) infiltrative mass in the upper pole of the right kidney.

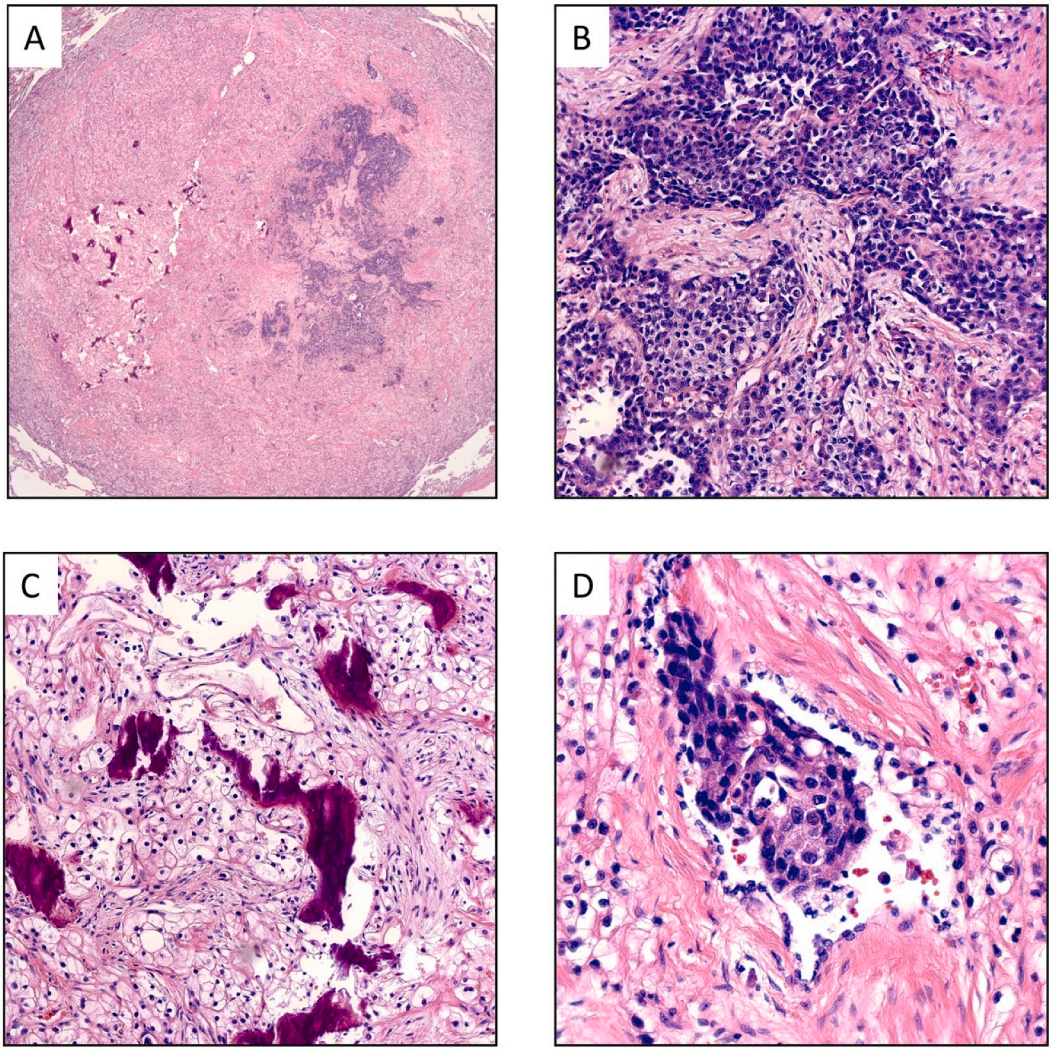

Fig. 2. (A) Histopathological examination of one of the collision tumors demonstrating two cellular components: a major clear cell component at the periphery and core representing metastatic clear cell RCC, and a central component with adjacent osseous metaplasia representing the HGUC (25X). (B) Solid sheets of cohesive cells representing the HGUC (200x). (C) Osseous metaplasia with surrounding the clear cell RCC (200x). (D) HGUC cells within the vasculature of the clear cell RCC component (400x).

"field cancerization" precipitated by carcinogenic events might instigate the development of different genetic aberrations among cancer stem cells of distinct origins (i.e. genetically distinct cell clones within a tissue) and hence prompting tumor development either in a synchronous or metachronous state [21]. To note, the concept of "field cancerization" has been first suggested by Slaughter et al. in 1953, who demonstrated that the occurrence of multiple independent tumors in 11.2% of the studied sample could not be by chance but due to a process of field cancerization [22]. A third theory postulates that one neoplasm induces a second primary or acts as a recipient of another metastasizing tumor, referred to as "tumor-to-tumor carcinogenesis" or "tumor-to-tumor metastasis" [1]. The latter was first described by Berent in 1902 [33]. To consider this theory, several criteria must be met according to Campbell et al. [34]: (1) existence of more than one primary tumor; (2) the recipient tumor must be a true benign or malignant neoplasm (with RCC being the most common recipient of tumor-to-tumor metastasis in malignant tumors [35]); (3) the neoplasm metastasizing to the recipient tumor should be a true metastasis with established growth; and (4) tumors that are proven to have metastasized via the lymphatic system are excluded [34,36–38]. For instance, some of the documented tumor-to-tumor metastases include: colorectal carcinoma metastatic to chromophobe RCC [36], neuroendocrine carcinoma of the pancreas to angiomyolipoma of the kidney [35], breast carcinoma metastasizing to a pheochromocytoma [39], lung adenocarcinoma to angiomyolipoma of the kidney [35], and cervical cancer and Burkitt lymphoma metastasizing to meningioma [40].

The collision tumor described herein represents a hematogenous spread of tumor-to-tumor metastasis. Because the three metastatic foci were found to be collision tumors, an intricate dialog between the RCC and HGUC must have developed to support the development of this peculiar tumor rather than encounter by chance. The distribution of tumor components suggests that the HGUC metastasized to metastases of clear cell RCC. The RCC cells were located at the periphery defining the tumor boundaries; while, the HGUC cells where in the core adopting the shape of vascular spaces and infiltrating the RCC tumor bed. For RCC, the lung represents the most common site for metastasis (45%) followed by bone (30%) and lymph nodes (22%) [41] via hematogenous spread [42]. RCC of the clear cell type is driven by abnormal hypoxia-inducible factor signaling causing hypersecretion of angiogenic growth factors, such as vascular endothelial growth factor and platelet-derived growth factor [43], promoting angiogenesis and cancer progression and metastasis. Tumor cells travel via the renal vein into the inferior vena cava reaching the lungs as a first step in the metastatic cascade before entering the systemic circulation [44]. Conversely,

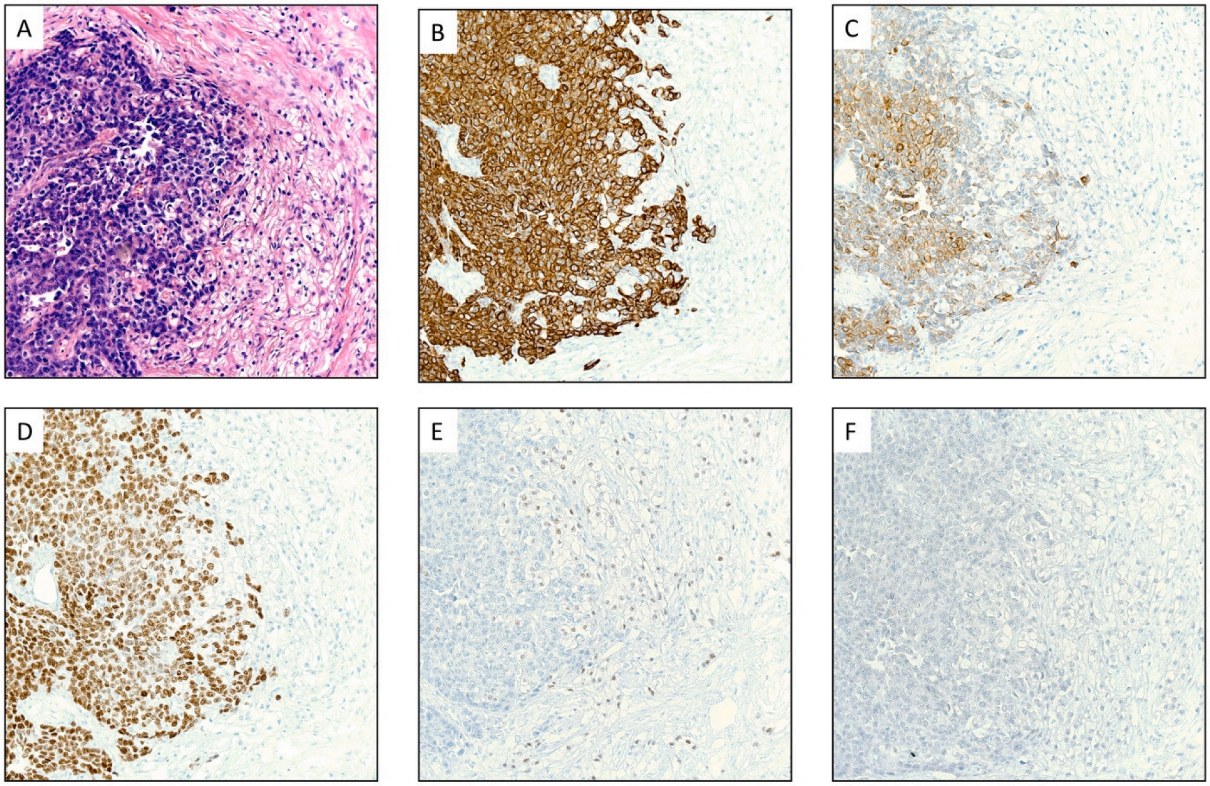

Fig. 3. (A) Hematoxylin and eosin (H&E) section showing HGUC component on the left and clear cell RCC on the right. (B) CK-7 staining the HGUC component. (C) CK-20 staining the HGUC component. (D) GATA-3 staining the HGUC component. (E) PAX 8 staining the nuclei of clear cell RCC. (F) TTF-1 showed negative staining in both HGUC and clear cell RCC components. All images examined at 200x.

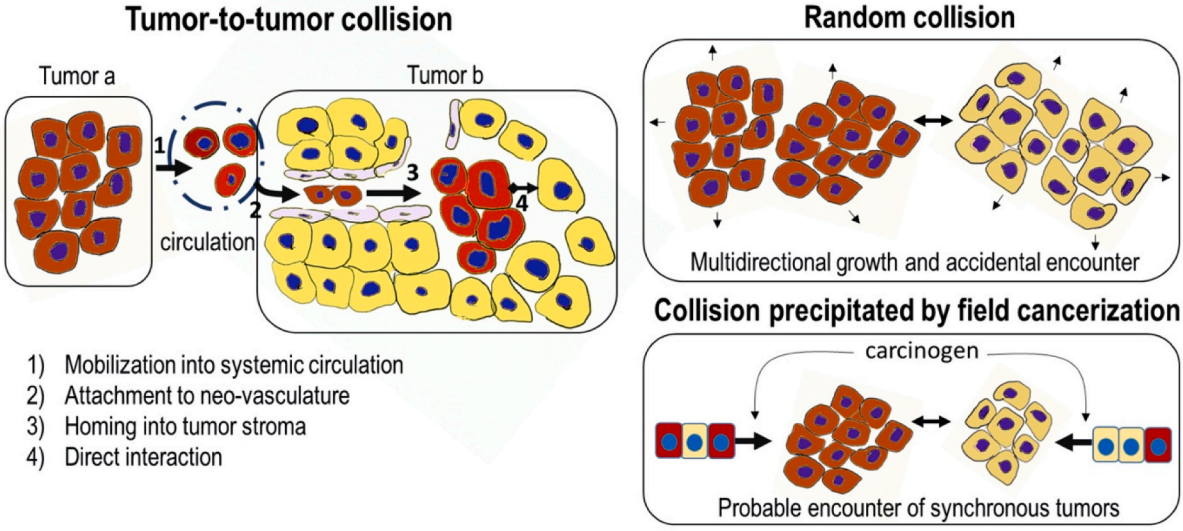

Fig. 4. Three theories proposed for the pathogenesis of collision tumor.

lymph nodes, bones, and lungs represent the most common sites of metastasis from bladder HGUC [45]. The signaling pathways implicated in the metastatic progression of HGUC are slightly different from those of RCC. Metastatic HGUC exhibit gene expression enrichment for epithelial-to-mesenchymal transition induced by numerous signaling pathways involving transforming growth factor (TGF)-β, integrins, Notch, Wnt, and sonic hedgehog [46–48]. HGUC may adopt a cancer stem cell phenotype, which is believed to be responsible for tumor metastasis and relapse [49,50]. Complex interactions of the cancer stem cell and tissue microenvironment [48] are ultimately thought to drive the process of metastasis.

Interestingly, the presence of heterotopic bone formation in the collision tumors could shed light on the conditions necessary to generate this peculiar phenomenon of metastases on metastases. Heterotopic

bone formation or osseous metaplasia is an uncommon, but well described, event in RCC and HGUC [51,52]. In both tumor types, the induction of an osteoblastic phenotype in the tumor stroma correlates with the overexpression of bone morphogenetic proteins (BMPs). The activation of BMP receptors triggers a signaling pathway with the nuclear translocation of SMAD transcription factors, similar to other members of the TGF-β superfamily. Induction of Notch and Wnt have also been described [53]. Some isoforms of BMPs have been linked to the promotion of EMT in several carcinoma models [54]. BMPs modulate different attributes such as cell movement, adhesion, invasiveness during the process of metastasis [53]. In this way, the development of osseous metaplasia in the RCC component of the collision tumors indicates that a distinctive tumor microenvironment could have coordinated the interaction between HGUC and RCC cells leading to the "metastasis to metastasis" formation.

4. Concluding remarks

Collectively, we propose that having HGUC colliding with RCC in the same location with a tumor-to-tumor growth pattern is not a random event and can be explained by distinctive tumor microenvironment interactions wherein crosstalk between both tumors might have occurred.

Ethics approval and consent to participate

The work described has been carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki).

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Author contributions

K.O. worked on the case report conception and contributed to the data collection. K.O. and VS contributed to the pathological slides review, selection of tissue for the molecular analysis, and data analysis. K.O. was responsible for getting the clinical data from medical records of the hospital and writing section "Case Presentation". VS provided other authors with explanations about the case reported. HFB worked on the histology figures, figure illustrations, and case study timeline presentation. HFB, CAFA and K.O. were responsible for writing the discussion and editing the whole manuscript, in addition to proofreading. VS and F.S. were responsible for the study supervision and conduction of the whole project. All authors critically revised and edited the manuscript prior to approving the final draft. All authors approved the final draft of the manuscript.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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