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# Hyaline vascular Castleman's disease (HVCD) mimicking lung metastasis of renal carcinoma: A case report and literature review

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ABSTRACT

Castleman's disease (CD) is a rare lymphoproliferative disorder characterized by atypical lymph node follicular hyperplasia. Subsequential occurrence of CD and cancers has been rarely reported and interpretations of the relationship are contentious. An asymptomatic 70-year-old man was found to have a left-sided hilar mass during routine follow-up after a radical right nephrectomy for clear cell carcinoma, raising suspicions of lung metastasis. Because there was no sign of recurrence in the original operative region, he underwent wedge resection of the left lung and lymph nodes dissection. Histology showed typical features of HVCD. Herein, we emphasize careful histopathology and complete resection of CD. We speculate that subsequential occurrence of CD and cancers may not be coincidental and warrants further exploration.



## Background

Castleman's disease is a rare atypical lymphoproliferative disorder, consisting of two main entities – UCD (Unicentric Castleman's Disease) and MCD (Multicentric Castleman's Disease) with different characteristics [1, 2]. Coexistence or subsequential occurrence of CD and other malignancies has been rarely reported, and explanations other than coincidence are contentious [3–8].

## Case presentation

An asymptomatic 70-year-old man was found to have an enhancing right renal mass during a routine workup in a computed tomography inspection (CT) (Fig. 1). A chest X-ray and all preoperative laboratory findings were normal. He underwent a radical right laparoscopic nephrectomy for suspected renal cell carcinoma. Gross pathology examination demonstrated a ductile, red and pale mass, limited to

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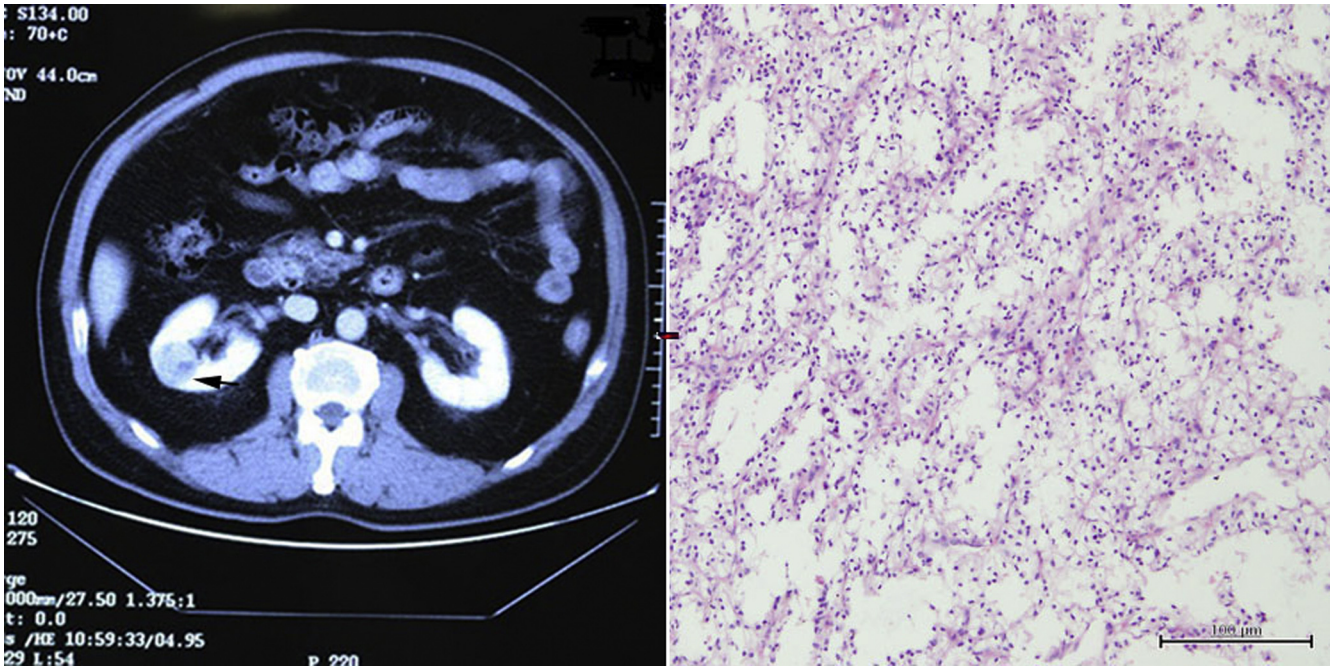

**Fig. 1 – Contrast-enhanced CT image of the abdomen showing an enhancing mass, highly suspicious for malignancy (as the arrow showed). Hematoxylin-eosin stained photo-micrograph shows typical pathology of clear cell renal cancer**

the right renal, measuring 3.2 cm × 2.8 cm × 3.0 cm. A clear cell carcinoma was confirmed on histology (Fig. 1). Observation was suggested as per National Comprehensive Cancer Center guidelines (Version 2. 2014). Follow-up CT and US (ultrasound) were normal until a CT (Figures not shown) demonstrated a distinct left-sided hilar mass two years postoperatively. A subsequent PET-CT (positron emission tomography/computed tomography) scan confirmed an abnormal soft tissue mass with increased 18F-FDG (18F-fluorodeoxyglucose) uptake in the inferior lobe of left lung near the diaphragm, raising suspicions of malignancy, but no sign of recurrence in the original operative region (Fig. 2). All preoperative laboratory findings including CRP (C reactive protein), ESR (Erythrocyte sedimentation rate) were normal. Etiologic testing including HIV (human immunodeficiency virus) antibody and HHV8 (human herpes virus 8)

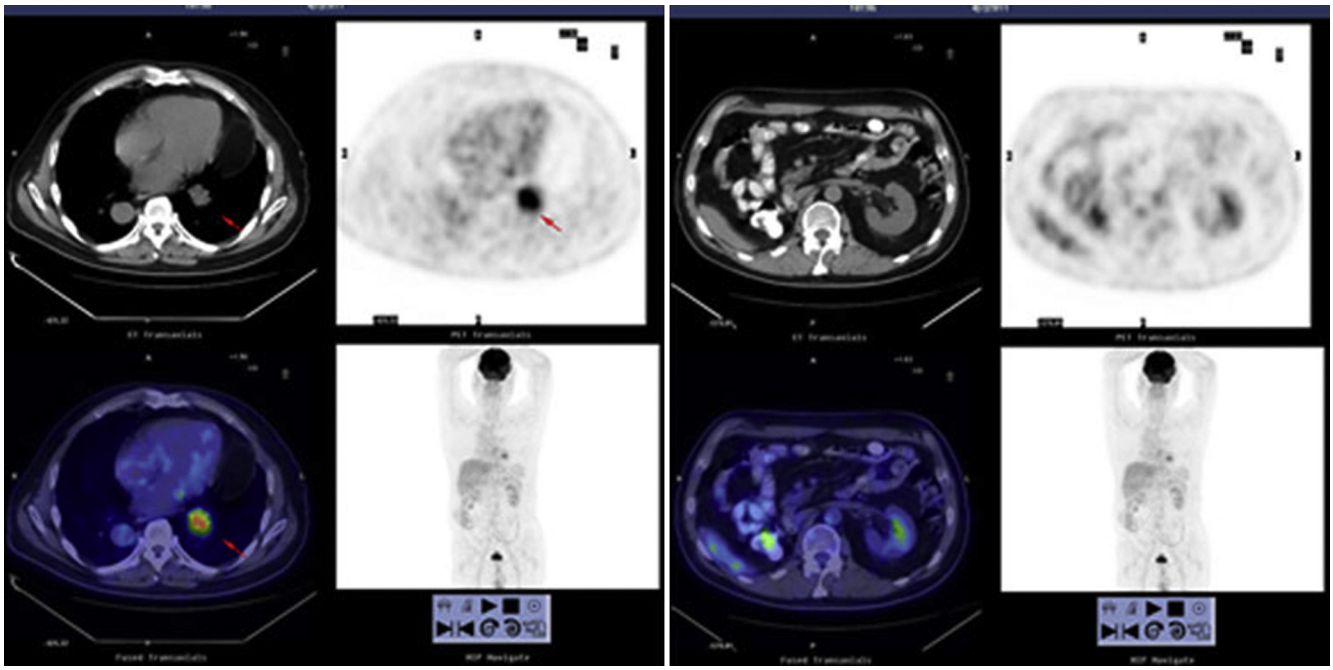

**Fig. 2 – An abnormal soft tissue mass with increased 18F-fluorodeoxyglucose accumulation suspicious for malignancy, with no evidence recurrence in the original operative region (as the arrows showed)**

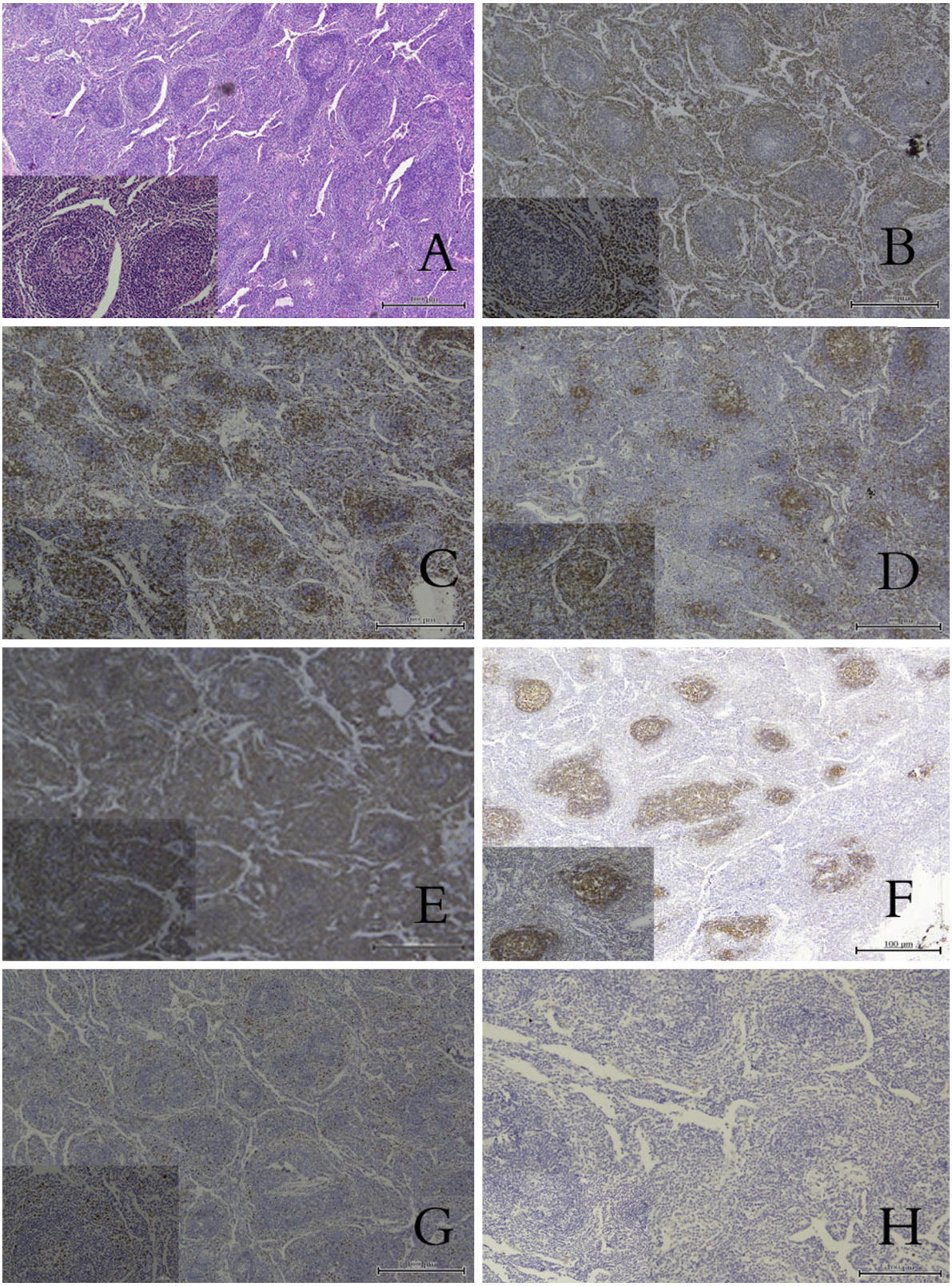


**Fig. 3 – (A) Typical histologic features of Castleman's disease with hyaline vascular variant. Hematoxylin–eosin stained photomicrograph shows the classic 'onionskin' appearance in immunohistochemistry. (B) Bcl-2 negative. (C) CD3 partially positive. (D) CD5 partially positive. (E) CD20 prominently positive. (F) CD21 follicular negative. (G) Ki-67 20% positive. (H) cyclinD1 negative (all of the photomicrographs are presented with magnification of 4× and 20×)**

were normal. To establish a definitive diagnosis and exclude lung metastasis, he underwent a wedge resection of the left lung and the 7, 9, 11 groups lymph nodes dissection. Histological sections of the mass revealed typical features of HVCD: many lymphoid follicles with hyalinized germinal centers and broad mantle zones, showing the classic 'onionskin' appearance, with vascular proliferation prominent in the germinal centers and the interfollicular areas in HE staining (Fig. 3A). The IHC (immunohistochemistry) showed blow (Fig. 3B–H), confirmed the HVCD histology. Observation and regular check-up were suggested. Until now, there is no sign of reoccurrence.

## Discussion

Benjamin Castleman first reported the rare lymphoproliferative disorder that bears his name in 1954 [1]. CD is a heterogenous disease separated into two entities clinically – UCD (unicentric Castleman's disease) and MCD (multicentric Castleman's disease), with distinct treatment algorithms and prognosis. CD is further divided into three variants histopathologically. The plasma cell and mixed type usually present as MCD, often associated with constitutional symptoms and require systematic therapy [5]. The hyalinized vascular type accounts for 90% of UCD, is often asymptomatic at presentation, and has a high cure rate with surgical excision [9]. Complete resection is required as recurrence following surgery does occur in a minority of UCD cases [10].

## Relation with cancers

While CD is a group of benign lymphoproliferative disorder, there are complex relationships between CD and malignancies. Although rapidly improving imaging techniques exists, especially PET-CT, may failed to differentiate CD and cancers. [11, 12]. Recent reports show that CD can mimic neoplasm causing diagnostic dilemmas requiring pathology to resolve [12, 13]. As in this case, diagnosis may be difficult to ascertain and should rely on histology.

Concomitant or subsequential occurrences of CD and malignancies including lymphoma, melanoma, Kaposi's sarcoma, melanoma, hepatocellular carcinoma and renal cancer have been reported [3–8]. It deserves consideration when a suspicious mass is present. In this case, CD in the mediastinum mimicked lung metastasis of renal cancer. Complete resection and careful pathology were needed to guarantee accurate diagnosis and therapy.

## Potential theories

Concomitant or subsequential occurrences of CD with cancers may be more than coincidental. A number of causal mechanisms have been proposed.

IL-6 is involved in a wide range of biologic activities, such as auto-immune disease, chronic inflammatory proliferative disease and apoptosis resistance [14]. Stimulating B lymphoid cell proliferation and plasma cell differentiation, high expression of IL-6 was discovered both in the lymph nodes and serum of CD patients, and fluctuation of IL-6 is correlated with symptom variation [15]. In recent case reports, Tissier and Deshmukh attributed CD synchronous with cancers to dysimmunity caused by IL-6 elevation [3, 4]. Often reported coexistent with MCD, Kaposi's sarcoma is commonly attributed to HHV-8 infection [16]. HHV-8 can encode viral IL-6 (vIL-6) in latently infected cells, which can initiate MCD by binding to ubiquitously expressed gp130 receptor submit and subsequently JAK-STAT pathway [17]. Research on hepatocellular malignancy showed that elevation of IL-6 is insufficient. Experiment in vivo suggests that a certain threshold of IL-6 stimulation is required to initiate hepatocellular hyperplasia [18], whereas a second hit of CTNNB1 (c.121A >G; p.T41A) mutation is necessary for the development of concurrence of hepatocellular carcinoma and CD [6]. Siltuximab (a chimeric human-murine anti-IL-6 antibody) has produced a favorable response in a case of cutaneous CD [19].

In addition to IL-6, evidence is accumulating that abnormal expression of VEGF (vascular endothelial growth factor) may be another factor [4, 8]. As an important hallmark of cancer, angiogenesis links the malignancy and distant metastasis, and frequently appears in the interfollicular space of CD. Closely correlated with vessel density, VEGF seems to be the most relevant cytokine in this respect. As for renal carcinoma, a VHL gene mutation often occurs, activating the hypoxia-response pathway and inducing transcription of several genes, including VEGF, and subsequent tumor progression [20]. Complete resection of CD may be essential to avert susceptibility to microangiopathy related to VEGF [21]. A single case report discusses the successful embolization with polyvinyl alcohol microparticles [22].

There are several reports of concurrence of follicular dendritic cell sarcoma (FDCS) with HVCD [23]. Follicular dendritic cells are a kind of stromal cells, dysplasia of which may provide a new pathogenetic hypothesis of HVCD [24]. Discoveries on the chromosomal level have provided genetic interpretations and give clues that complication of HVCD and FDCS may not be coincidental [25].

An intriguing question emerges: does CD contribute to the development of cancers or vice versa? CD was considered a paraneoplastic phenomenon of spindle cell carcinoma [5]. When it coexisted with Hodgkin's disease, it was regarded as a reaction to malignancy [7]. In a case of occurrence with melanoma, CD was proposed to be a consequence of VEGF secretion by solid tumors [8].

## Conclusion

This case of HVCD mimicking lung metastasis of renal clear cell carcinoma required careful histopathology and complete resection of CD. This coexistence of CD and cancer may not be a coincidence. Further research is warranted to unmark the relevant occult mechanism.

## Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

## Authors' contributions/Wkład autorów

The study was designed and data were collected by SC and XBR. Statistical analysis and manuscript preparation were done by AYQ. Data interpretation and literature search were performed by AYQ.

## Conflict of interest/Konflikt interesu

None declared.

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## Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical Journals.

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