Coexistence of Unicentric Castleman’s Disease and Locally Advanced Papillary Renal Cell Carcinoma: More Than a Coincidental Association?

Dear Editor,

Castleman’s disease (CD) is an enigmatic lymphoproliferative disorder due to its rarity, uncertain aetiopathogenesis and heterogeneous clinicopathologic forms. This case report presents an unusual case of concomitant hyaline-vascular type CD of unicentric retroperitoneal localisation and stage IV (T2N2M0) papillary renal cell carcinoma (RCC).

Case Report

A 35-year-old Chinese male was presented with left-sided abdominal pain associated with gross haematuria but with no constitutional symptoms. Physical examination was unremarkable. Full blood count showed haemoglobin 12.0 g/dL, white cells 11,300/μL with normal differential counts, and platelets 803,000/μL. Serum protein was 64 g/L, albumin 32 g/L and calcium 2.31 mmol/L. Hepatic and renal profiles were normal.

Computed tomography (CT) urogram revealed a 7.1 cm x 7.7 cm x 8.1 cm mass arising from the left renal upper pole, with enlarged para-aortic nodes. There was also an enhancing nodal mass between the inferior vena cava (IVC) and the portal vein origin, measuring 3.9 cm x 2.4 cm x 4.3 cm with central dystrophic calcification. Staging workup was negative for pulmonary and bony metastases.

He underwent an open left radical nephrectomy with renal perihilar lymph node dissection and precaval lymph node dissection. Intraoperative findings were of a 10 cm x 8 cm left renal tumour not involving Gerota’s fascia, renal vein and IVC; a 6 cm x 4 cm hard node at the portocaval window adjacent to the pancreatic head extending to the aortocaval space; and a 4 cm x 2 cm perihilar lymph node. Histology showed a papillary type 2 RCC, 7.7 cm in greatest dimension (T2) and Fuhrman nuclear grade 3/4. Three out of 4 perihilar lymph nodes harboured metastatic disease (N2).

The gross specimen of the portocaval node consisted of a piece of adipose tissue containing a central hard bony nodule measuring 1.2 cm x 1.1 cm x 1 cm. Microscopically, it exhibited characteristics of hyaline-vascular type CD with calcification and ossification, as well as focal lipophagic reaction (Fig. 1).

The patient was later screened negative for human immunodeficiency virus (HIV). Unfortunately, he relapsed with metastatic disease in his supraclavicular lymph node 19 months after the nephrectomy.

Discussion

CD can be classified as: (i) unicentric (UCD) versus multicentric (MCD), (ii) hyaline vascular (HV), plasma cell (PC), mixed cellularity (HV-PC) or plasmablastic subtypes,1,2 and (iii) HIV-negative versus HIV-positive.

Unicentric HV-CD affects young adults more frequently, typically occurring as an isolated nodal mass or regional adenopathy. The mediastinum and pulmonary hilum are commonly involved (70%), followed by the neck (14%), abdomen (12%) and axillae (4%).1

Radiologically, the lesions in unicentric HV-CD are hard to distinguish from other tumours, particularly hypervascular and/or calcified ones. Calcification patterns of CD in the abdomen and pelvis include punctuate, coarse, peripheral and arborising. Central dystrophic calcification was seen in our patient.

A definitive diagnosis of CD necessitates tissue biopsy. The HV subtype demonstrates the most specific histomorphologic features of the 4 variants: (i) expanded mantle zones composed of circumferentially arranged
lymphocytes surrounding involuted germinal centres, (ii) small hyalinised vessels penetrating germinal centres, (iii) hypervascular interfollicular stroma and sinus effacement, (iv) and diffuse interspersion of dysplastic follicular dendritic cells.\(^1\,2\)

UCD usually follows a benign clinical course and surgical extirpation is curative.\(^1\,3\) Our patient had clinicopathologic features compatible with the diagnosis of unicentric HV-CD.

The most poorly comprehended aspect of CD is its aetiopathogenesis. Casper proposed a developmental model,\(^1\) with the initial event being interleukin-6 (IL-6) expression by B cells in the nodal mantle zone. This is precipitated in most cases by human herpes virus 8 (HHV-8) infection, and in the minority by a hitherto unidentified exogenous or endogenous factor. Local elaboration of IL-6, and in turn vascular endothelial growth factor (VEGF), causes B-cell proliferation and hypervascularisation. The systemic effects in MCD may be consequent upon circulating IL-6 or IL-6-producing B cells, excess antibody generation or disseminated HHV-8 infection.

MCD is classically associated with Kaposi’s sarcoma, non-Hodgkin’s lymphoma and epithelial neoplasia. The coincidence of CD with other neoplasms has been documented in sporadic case reports. Notably, Tissier et al\(^4\) reported a 65-year-old woman with renal chromoprobe cell carcinoma and inter-aorticocaval adenopathies diagnosed as MCD. They hypothesised that neoplasia could develop in the setting of dysimmunity, or that their patient’s MCD might be associated with IL-6 production by her RCC.\(^4\) Their first premise mirrored those of authors of earlier papers.

Although these hypotheses were made with reference to MCD rather than UCD, parallels can still be drawn between the uni- and multicentric forms pertaining to immune defects inherent to CD. This is evidenced by autoimmune associations of UCD, e.g. paraneoplastic pemphigus and thrombotic thrombocytopenic purpura.\(^1\,3\) It, therefore, remains plausible that a state of immune dysfunction might have existed in our patient with unicentric HV-CD and played a part in carcinogenesis.

The concept of a bidirectional pathogenetic link between UCD and RCC is attractive too. Applying Casper’s model,\(^1\) RCC might have produced certain ‘exogenous’ factor(s) conducive to the advent of UCD in our patient. Two such putative paracrine factors are IL-6 and VEGF. IL-6 is less promising, considering that abnormally elevated levels of IL-6 are found only in patients with MCD, and that our patient lacked the systemic manifestations expected with freely circulating IL-6. Conversely, VEGF could prompt, at amenable sites, angiogenesis which may be an important step in the causal pathway of CD.\(^1\,2\) That said, the identity of the candidate factor(s) remains open-ended and we did not assay levels of IL-6, VEGF or other substrates in our patient’s serum and operative specimens.

**Conclusion**

The rarity and heterogeneity of CD have limited thorough understanding of its aetiopathology and management. A nodal mass in coexistence with a malignancy on computed tomography (CT) imaging more often than not draws suspicion of metastasis. Thus the diagnosis of CD must be confirmed through histopathology.

While CD is not associated with a higher incidence of carcinomas, case reports highlight the possibility of concomitancy with the latter. We presented such a case in which the unicentric form of disease was an incidental, asymptomatic finding in a patient with locally advanced RCC, and concurred with previous authors that this association might have arisen from a mutualistic pathogenetic basis rather than by chance.

**REFERENCES**


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