Unicentric Castleman disease in the paediatric neck: an unusual case of a rare diagnosis

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We present a rare case of unicentric Castleman disease (CD) in the paediatric neck. A 12-year-old Caucasian girl was referred to us due to a slowly enlarging, painless right-sided neck mass. Our thorough investigative approach identified unicentric CD, with previously undocumented CD-like features occurring simultaneously in a separate lesion from the lymph node group involved in unicentric CD. Recognition of CD in the paediatric patient is essential, despite the condition's rarity, to ensure adequate diagnostic work-up and management. We discuss features of unicentric CD, current concepts surrounding histology of the two separate variants of unicentric and multicentric CD, and the implications for management.

Keywords:
giant lymph node hyperplasia, herpesvirus-8 human, HHV-8, IL-6, multicentric Castleman's disease, neck, otolaryngology

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Introduction

Castleman disease (CD) is a lymphoproliferative disorder of unknown origin with two clinical variants: unicentric and multicentric. Unicentric CD typically presents as an indolent solitary mass, commonly within the mediastinum [1]. Generalised lymphadenopathy with systemic features characterise multicentric disease [2]. Histologically, unicentric CD has hyaline-vascular (80% of cases), plasma-cell or mixed subtype; multicentric CD is almost universally plasma-cell subtype. With only 29 case reports of paediatric neck CD [1,3], its incidence and natural history are poorly recognised, risking late or misdiagnosis [4].

Case history

We present the case of a 12-year-old girl with CD; speculating that the two clinical variants are less distinct than previously reported and highlight the importance of considering this rare differential diagnosis of paediatric neck mass.

A 12-year-old girl presented with a 4-month history of slowly enlarging, painless right-sided level II neck mass and fatigue. The mass was not tethered to the skin and appeared fixed to underlying structures. Systemic examination was unremarkable.

Ultrasound detected a 19×14 mm right upper jugular region lymph node. Incisional biopsy specimens were indicative of CD, hyaline-vascular subtype. Extensive haematological, biochemical and immunological blood tests were unremarkable. Serum interleukin-6 (IL-6) levels were normal.

The supraregional paediatric oncology multidisciplinary team agreed that further imaging was required to ensure diagnostic certainty. Abdominopelvic ultrasound was unremarkable. MRI of the neck and mediastinum revealed a 34×21×43 mm nodal mass, deep to the right sternocleidomastoid. Additional nodes were detected immediately inferior within the posterior triangle; measuring 6, 7, and 9 mm in their longest axis, respectively. A separate 28×18 mm left level IV/VII mass was identified inferior to the thyroid and posterosuperior to the sternoclavicular joint (Figs 1 and 2).

All suspicious tissue was surgically excised en-bloc through two separate transverse incisions. Histopathology of the right level II specimens showed normal lymph node architecture with prominent lymphoid follicles and regressed germinal centres surrounded by mantle zone. Some follicles showed multiple germinal centres surrounded by expanded mantle zones, with onion skinning of these mantle zones. Some germinal centres appeared atretic and were associated with a hyalinised vessel (Fig. 3).

Immunohistochemical staining for CD21 showed significantly hyperplastic and expanded follicular dendritic cell meshworks with concentric appearances, confined within follicles. Human herpesvirus-8 (HHV-

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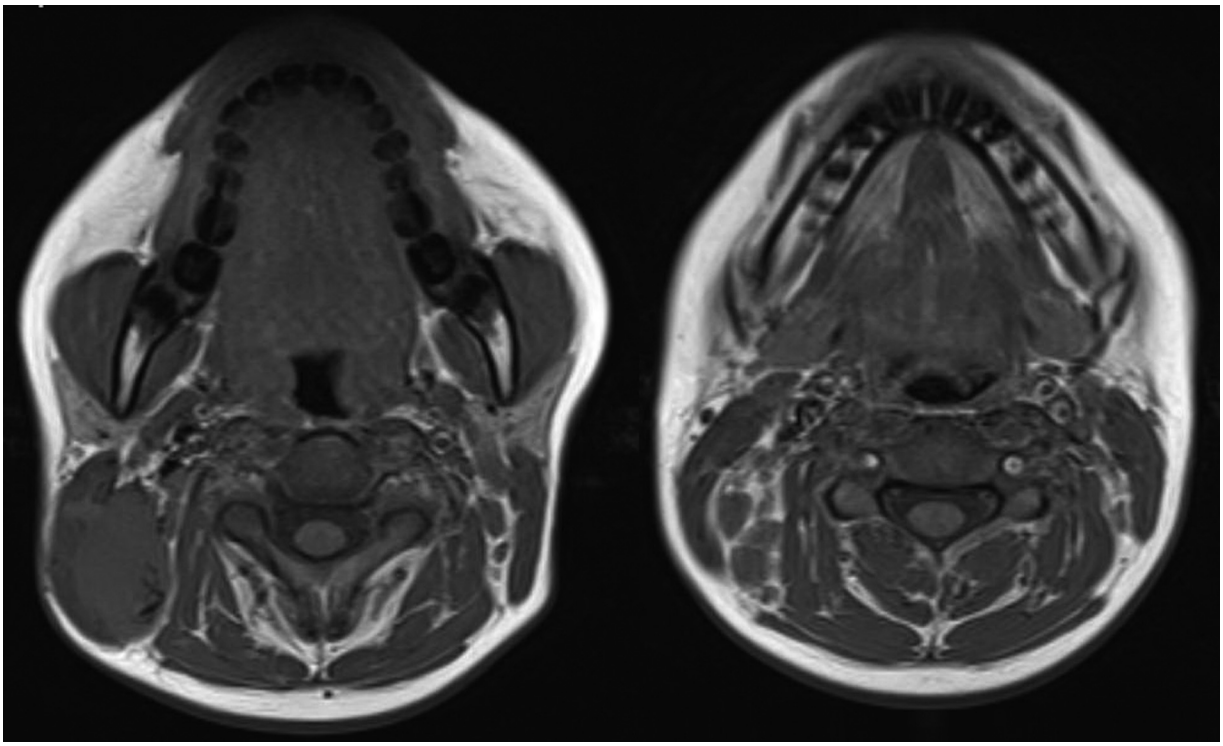
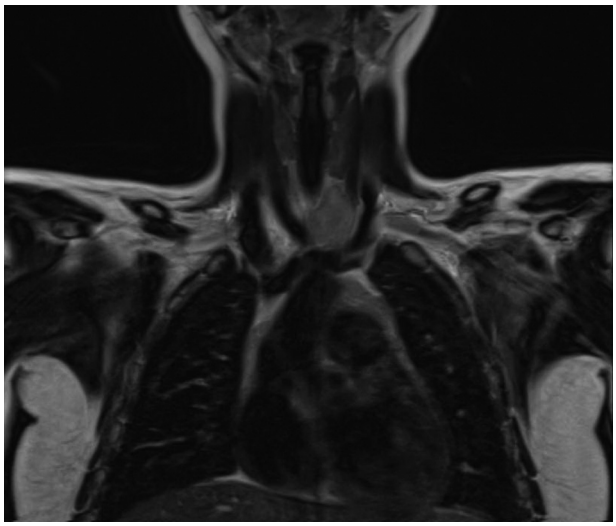
Figure 1



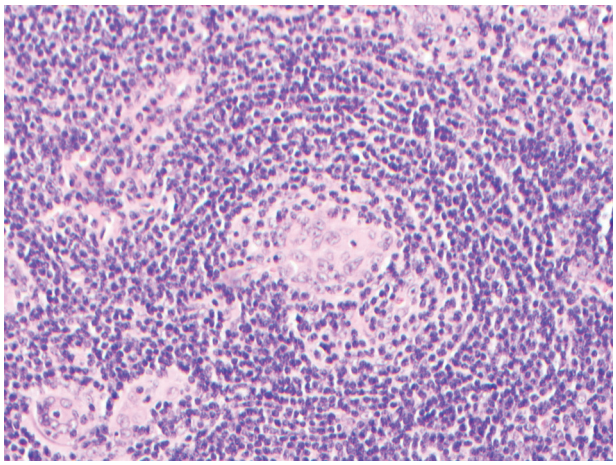
MRI of the Neck (axial view). (a) Level II lymph node deep to right sternocleidomastoid. (b) Right neck nodes in the posterior triangle (original).

Figure 2



MRI of the neck and mediastinum (coronal view). A left-sided level IV neck mass is visible (original).

Figure 3



Histological slide from the level II tissue specimen showing a germinal centre with an atretic appearance and associated onion skinning of the surrounding mantle zone (×20 magnification, haematoxylin and eosin stain, original).

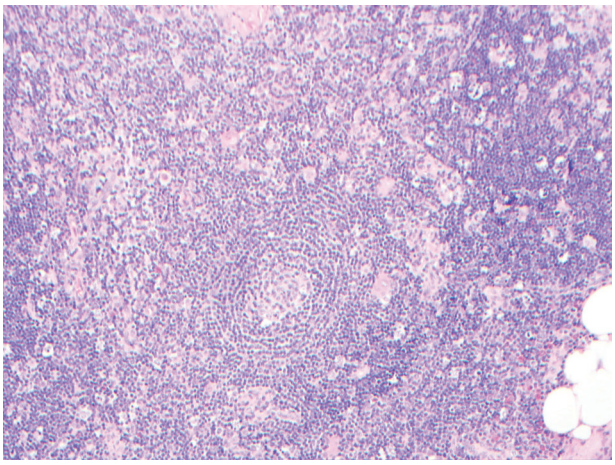
8) was not expressed. The appearances were entirely in keeping with CD of hyaline-vascular subtype. The left level IV/VII specimen was ectopic thymic tissue with preserved architecture containing Castleman-like features, occasional follicles with depleted germinal centres and onion skinning of the mantle zones. CD21 staining highlighted slightly prominent follicular dendritic cell meshworks in occasional follicles with concentric pattern (Fig. 4).

A diagnosis was made of unicentric CD with a hyaline-vascular histological subtype. The neck incisions healed well with all cranial nerves intact. No evidence of recurrent disease was present at 1 year.

Discussion

CD is exceptionally rare in the paediatric population. Patients with hyaline-vascular unicentric CD typically remain asymptomatic until a mass presents or causes

Figure 4



Histological slide from the level IV tissue specimen showing a follicle with a depleted germinal centre and onion skinning of the mantle zone (×10 magnification, haematoxylin and eosin stain, original).

compression of local structures. The rarer plasma-cell subtype frequently presents with systemic symptoms, similar to multicentric disease [5,6]. Casper [3] suggested a workup model for the investigation of CD. In our case, MRI and ultrasonography of the mediastinum and abdomen identified additional neck lesions and a contralateral level IV/VII mass with CD-like features. This supports a thorough investigative approach, even if initial work-up suggests unicentric disease. Current evidence suggests a good long-term prognosis for unicentric hyaline-vascular CD, as suffered by our patient. Surgery is diagnostic and therapeutic, with low rates of disease recurrence [1].

Proinflammatory cytokine IL-6 and HHV-8 infection are implicated in the pathogenesis of CD [5,7]. HHV-8 produces a viral analogue of IL-6. IL-6 is produced intrinsically by the germinal centres of hyperplastic lymph nodes in CD and causes lymphocyte proliferation [8]. IL-6 serum levels are high in multicentric CD and the plasma-cell variant of unicentric CD [3], and levels correlate with the presence of systemic symptoms [9]. There is evidence that IL-6 targeting immunomodulatory drugs provides therapeutic benefit and improves outcomes in multicentric disease [9].

Our patient was HHV-8 negative with normal serum IL-6 levels, in-keeping with unicentric CD of hyaline-vascular subtype. The blood mononuclear cells exhibited high production of IL-6 after activation by toll-like receptor agonists and mitogen; the significance of this finding is uncertain in the context of normal serum IL-6 levels. We speculate that the Castleman-like features found in the contralateral neck mass were a precursor to multicentric disease, and IL-6 upregulation is a critical factor in this process.

Unicentric CD normally involves one lymph node or a single chain of nodes. In our patient, a chain of level II lymph nodes was involved but, additionally, CD-like features were identified in a contralateral level IV/VII mass. The importance of the CD-like features is unknown, but their presence in the context of the patient's significant fatigue may represent early transformation of the disease toward the multicentric variant.

This report augments the small evidence base for paediatric CD and develops discussion around the pathogenesis, clinical course and management of unicentric disease. This case raises new questions about the pathogenesis and clinical course of this poorly understood disease. It is the only case to report CD-like features in a satellite lesion, with hyaline-vascular CD as the primary disease. Our thorough investigative approach allowed identification of the level IV lesion; therefore, we recommend extended body-imaging in these patients. A normal serum IL-6 level in our patient gave reassurance of the diagnosis of unicentric CD. We suggest this biomarker, which is characteristically raised in the multicentric variant [3], be used to help differentiate unicentric from multicentric disease in future patients.

The significance of the CD-like features in our patient's level IV/VII lesion is unclear and requires further investigation, particularly into the natural history of CD, the role of IL-6 and whether unicentric CD can silently transform into the multicentric variant.

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Conflicts of interest

There are no conflicts of interest.

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