Weill Cornell Medicine
Dermatopathology

The Histopathologic Spectrum of Cutaneous Castleman Disease

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ASDP 62nd Annual Meeting
11.7.25

Disclosures

- **I do not have any relevant financial disclosures**

Castleman Disease

LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA RESEMBLING THYMOMA

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IN the course of studying tumors of the thymus gland we came across a small group of cases in which enlarged mediastinal lymph nodes resembled thymic tumors grossly, radiologically, and even microscopically; and they had been so classified. We wish to report a series of thirteen cases from the Massachusetts General Hospital, the Armed Forces Institute of Pathology, and the University of Havana, as well as individual cases from various pathologists. Case 1 has previously been reported in the Case Records of the Massachusetts General Hospital;[2] cases 9 and 13 were included in a paper given by one of us (L.I.) before the American Association of Pathologists and Bacteriologists[3] and a brief description of the condition was included in the fascicle on *Tumors of the Thymus Gland*.[1] Cases 5 and 10 have been reported as thymomas[3, 4] (we believe erroneously).

Clinically most of these patients had no symptoms, the mediastinal shadow being discovered on a routine chest roentgenogram (Figs. 1,A; 2,A; 3; 4; 5,A). A few of the patients consulted their physician because of frequent colds and cough. There was no history of weakness or symptoms suggesting myasthenia gravis. There was no sex predominance and their ages ranged from 19 to 54 years. The benign character of the lesion is attested to by the fact that some had been present without change in size (radiologically) for as long as eight years and that there have been no recurrences locally nor any evidence of other lesions elsewhere after removal of the mass.

At operation only two of the masses were located in the mid-superior anterior mediastinum where the thymus gland usually is located. The others were to either the right or left of the mid-line, usually at a lung root, around one of the great vessels, or close to an interlobar fissure. In one case the lesion presented as a supraclavicular mass. Although in most cases the lesion proved to be a single mass, in a few cases it was composed of one large and two or three smaller adjacent masses, the latter looking more like enlarged lymph nodes than did the larger mass (Fig. 1,B,C).

When sectioned, the tissue was soft, smooth, and homogeneously gray-red. Some were very hemorrhagic and probably accounted for the excessive bleeding encountered by the surgeons.

Microscopically there were two prominent features: hyperplasia of lymphoid follicles with and without germinal-center (secondary-nodule) formation and marked capillary proliferation with endothelial hyperplasia. With respect to the lymphoid follicles, there were all stages from the characteristic follicle in which the central half was composed of a germinal center with lymphoblasts and reticulum cells (Figs. 6, 7) to the follicle into which capillaries had penetrated and appeared as radiating sprouts (Fig. 8). When these intrafollicle capillaries with hyperplastic endothelium had thick hyalinized walls they often assumed a concentric arrangement, which was accentuated where the capillary lumina were obliterated (Figs. 9, 10, 11). It is this combination of changes that makes it resemble the Hassall corpuscle of the thymus; especially when in some follicles only fragments of the capillary walls appear as hyalin foci. The characteristic staining qualities of keratin normally found in the Hassall corpuscles were not observed. In some cases hyalin foci outside of the follicles were undoubtedly pinched off strands of the hyalinized connective-tissue septa extending into the node from the capsule. These also did not stain like keratin.

As already mentioned, the nodes were very vascular grossly and this was borne out micro-

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The authors wish to thank Dr. E. R. Crane, Pennsylvania Hospital; Dr. J. R. McDonald, Mayo Clinic; J. R. Houghton, Boston Veterans Administration Hospital; and L. Ackerman, Barnes Hospital, St. Louis, for permission to use cases 5, 6, 7, and 8 respectively.

Received for publication, January 9, 1956.

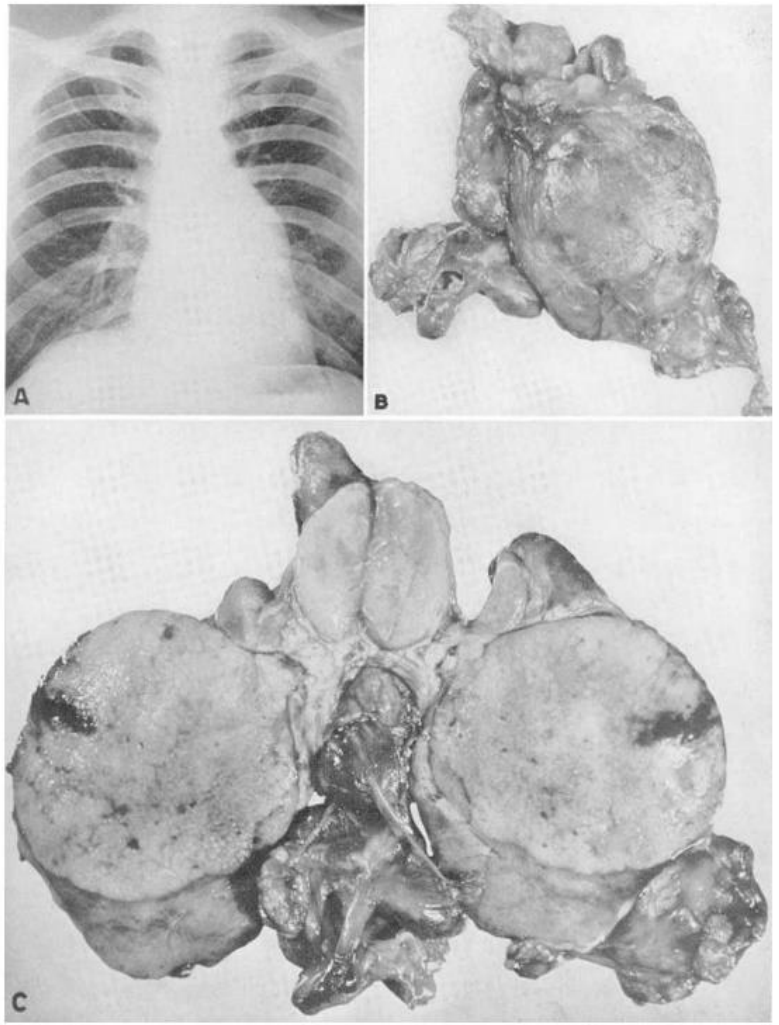


FIG. 1. Case 1. A, Chest roentgenogram showing left anterior mediastinal shadow. B, The mediastinal mass is composed of multiple discrete lymph nodes of varying sizes. C, Cut surfaces of larger nodes showing homogeneous smooth appearance.

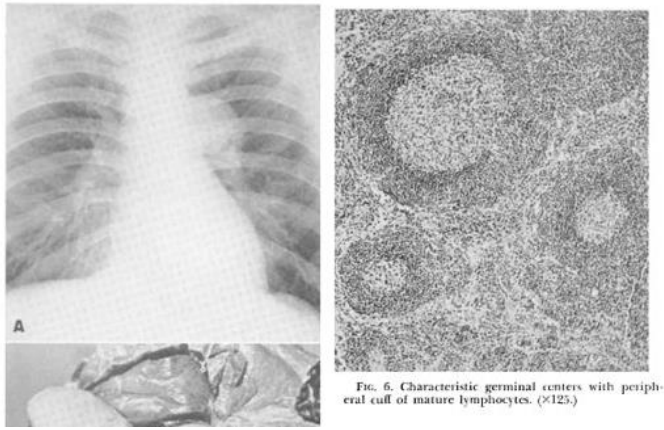
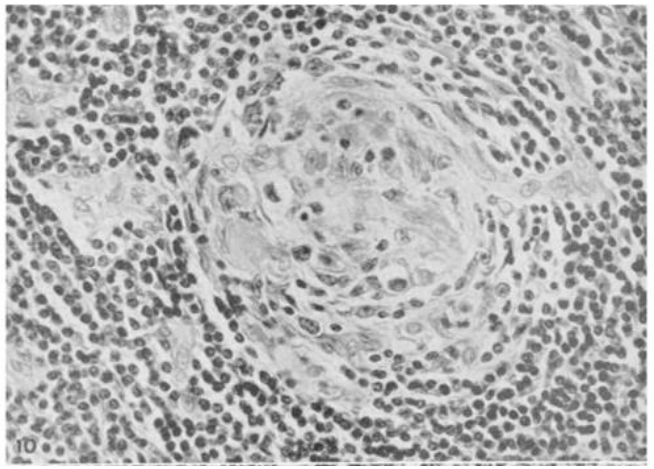


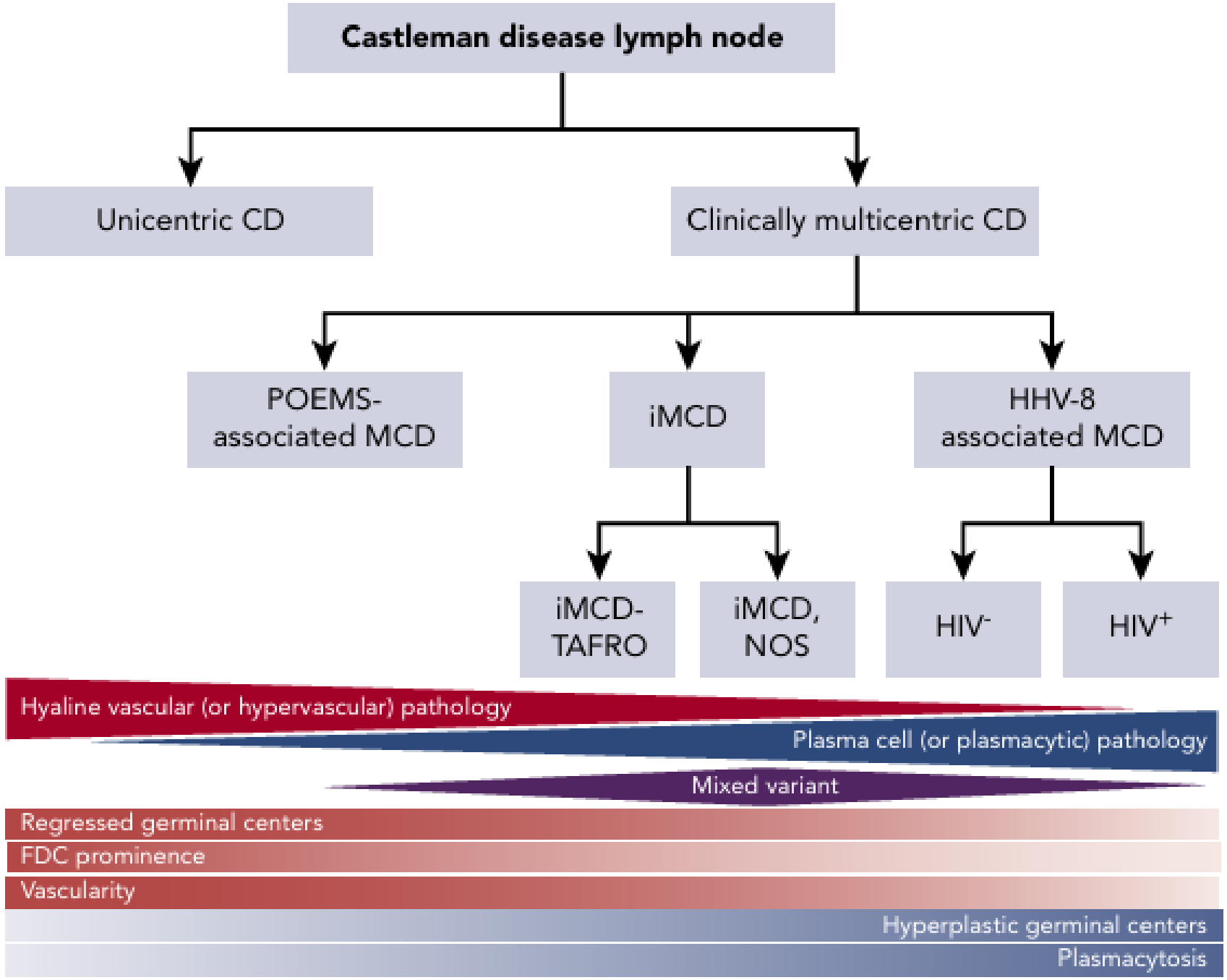
FIG. 6. Characteristic germinal centers with peripheral cuff of mature lymphocytes. (×125.)



Castleman Disease Overview

Unicentric Castleman Disease *(UCD)*	**HHV-8-associated Multicentric Castleman Disease** *(HHV-8+MCD)*	**HHV-8-negative "Idiopathic" Multicentric Castleman Disease** *(iMCD)*
▪ Single enlarged LN ▪ Idiopathic; few to severe symptoms (if para-neoplastic pemphigus or cannot be resected) ▪ Surgical excision is usually curative ▪ Unresectable UCD behaves like iMCD and should be treated systemically ▪ 90-95% 5-year survival	▪ Multiple regions of enlarged LNs ▪ In immunosuppressed, Human Herpes Virus-8 (HHV-8) drives cytokine release, notably IL-6 ▪ Causes flu-like symptoms and multiple organ system impairment (renal failure, pancytopenia, fluid gain) ▪ HHV-8 lives in B-cell ▪ B-cell elimination with or without antivirals are effective	▪ Multiple regions of enlarged LNs ▪ Unknown cause drives cytokine release, notably IL-6 ▪ Causes flu-like symptoms and multiple organ system impairment ▪ Unknown pathologic cell ▪ Siltuximab and chemotherapy can be effective; relapses common ▪ 65% 5-year survival

Fajgenbaum D, van Rhee F, Nabel C. *Blood*. 2014;123(19): 2924-2933.



TAFRO:

- **Thrombocytopenia**
- **Anasarca**
- **Fever**
- **Reticulin fibrosis**
- **Organomegaly**

POEMS:

- **Polyneuropathy**
- **Organomegaly**
- **Endocrinopathy**
- **Monoclonal protein**
- **Skin changes**

Dispenzieri A, Fajgenbaum D. Blood. 2020;135(16): 1353-1364

Materials and Methods

- **Retrospective review of WCM dermatopathology archives (2000–2024)**
  - **Nine patients with cutaneous CD (8 UCD; 1 MCD) identified**
  - **Sex: 5F / 4M; Mean age: 42.8 years (range 5–82)**

Unicentric Castleman Disease of the Skin

- **Majority of cases with single enlarged LN present in subcutaneous fat**
- **Most present with the hyaline vascular subtype, though mixed presentations are seen**
- **Represents an extranodal form of UCD**
- **Surgical excision is usually curative**
- **Unresectable UCD behaves like iMCD and should be treated systemically**
- **90-95% 5-year survival**

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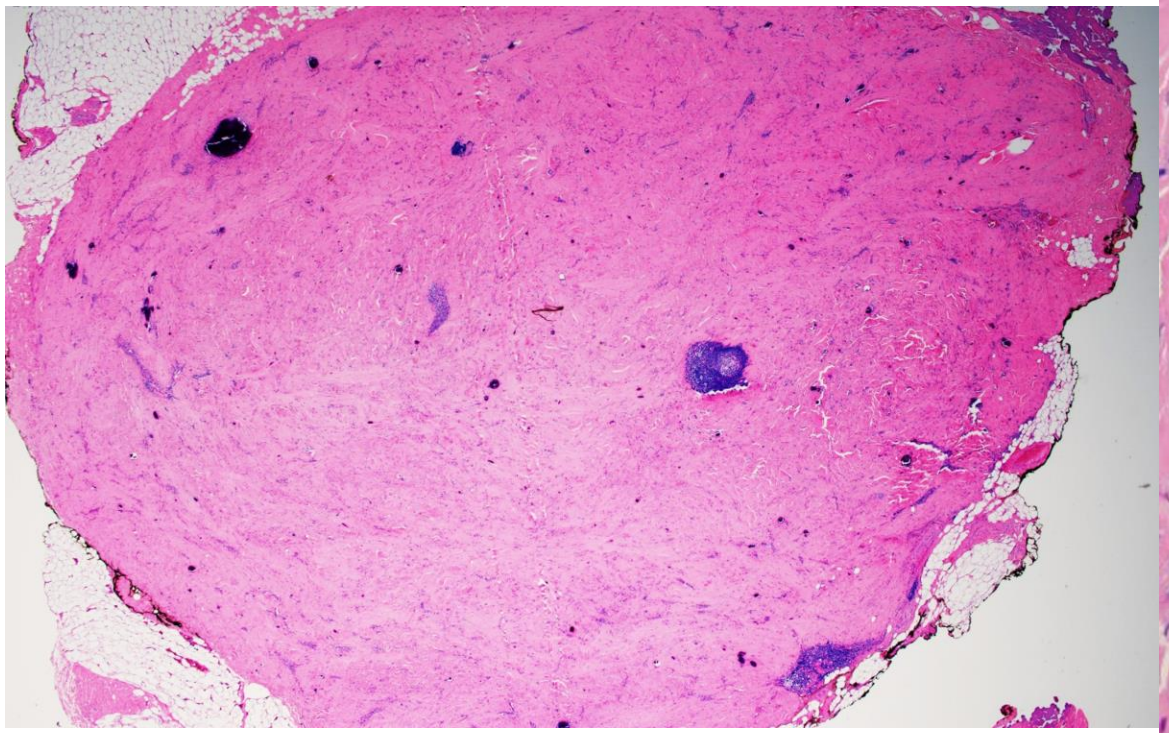
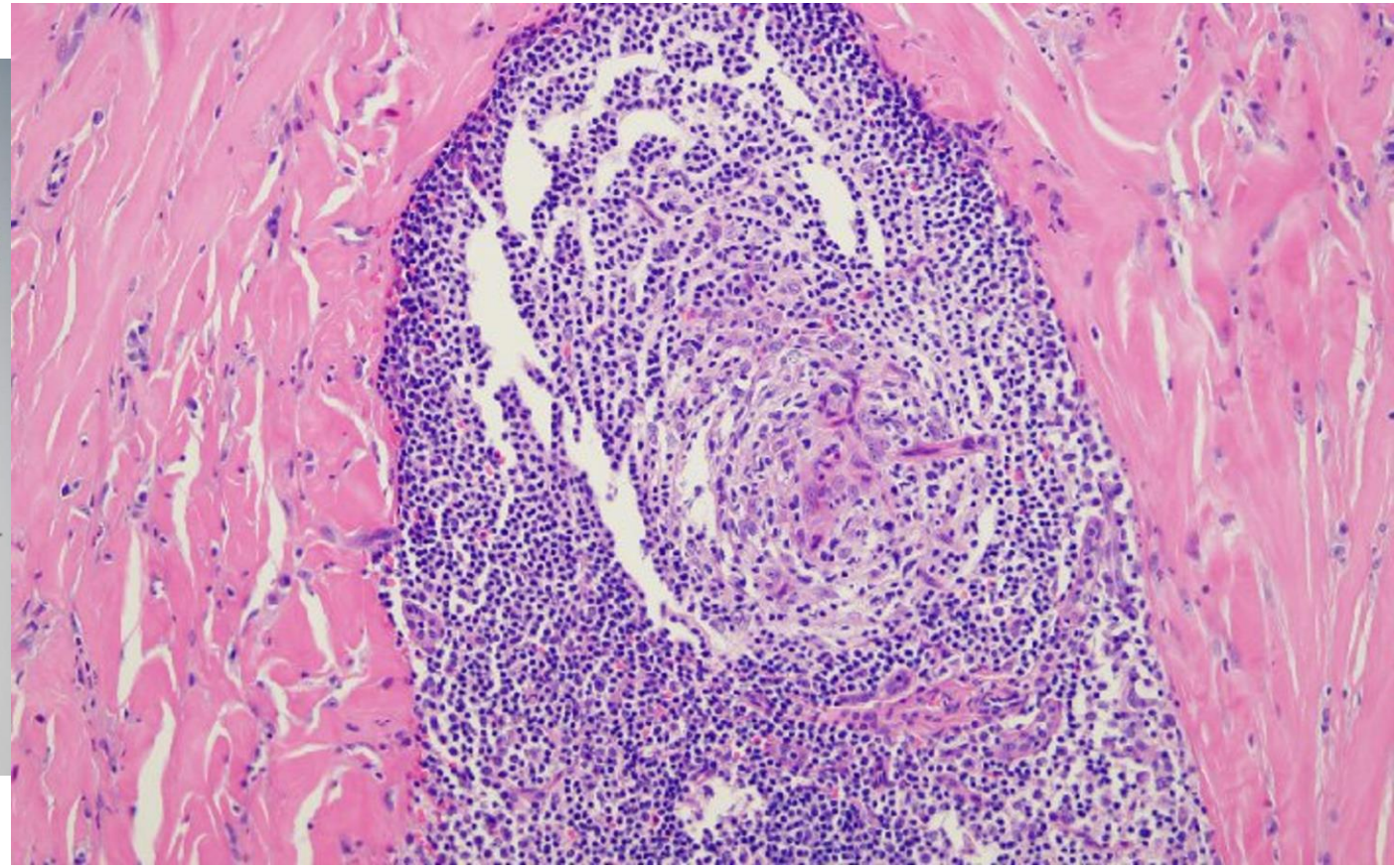
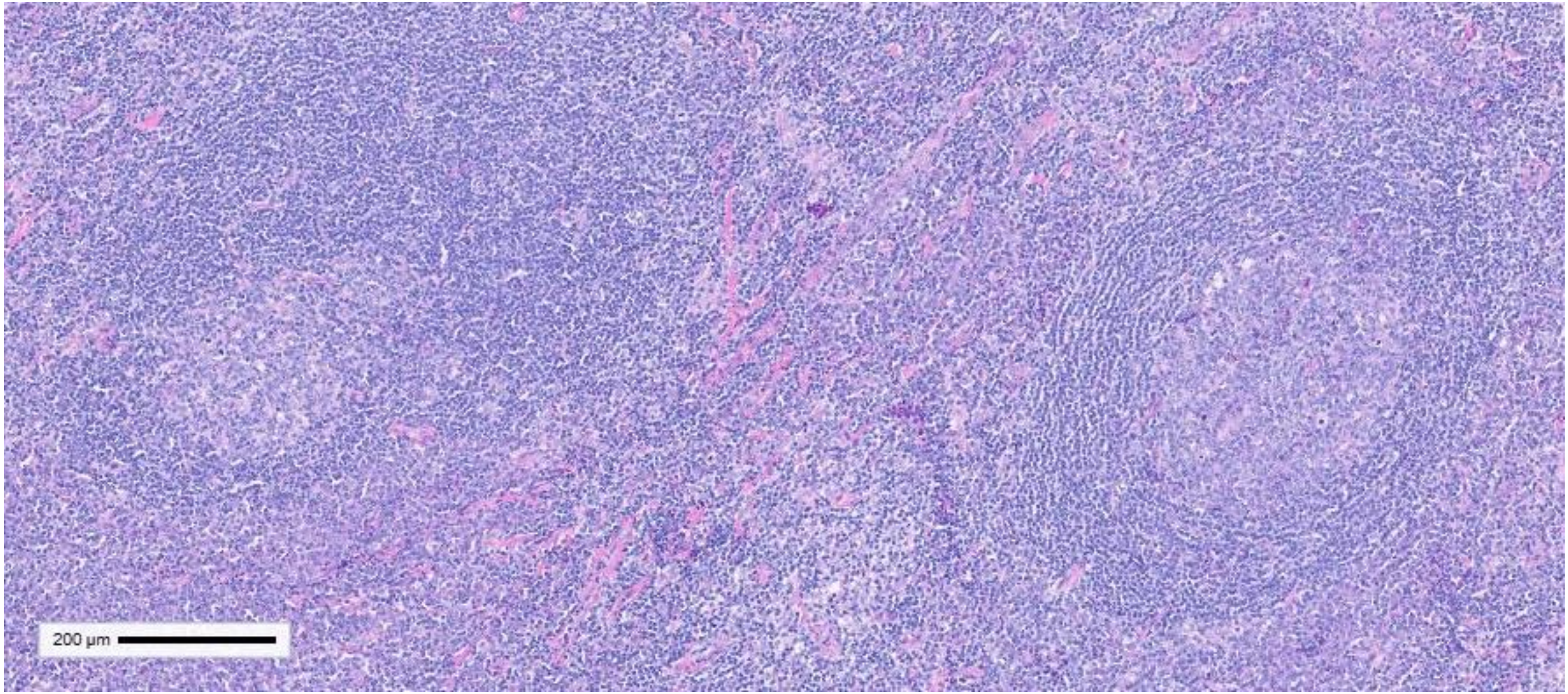
Unicentric Castleman Disease



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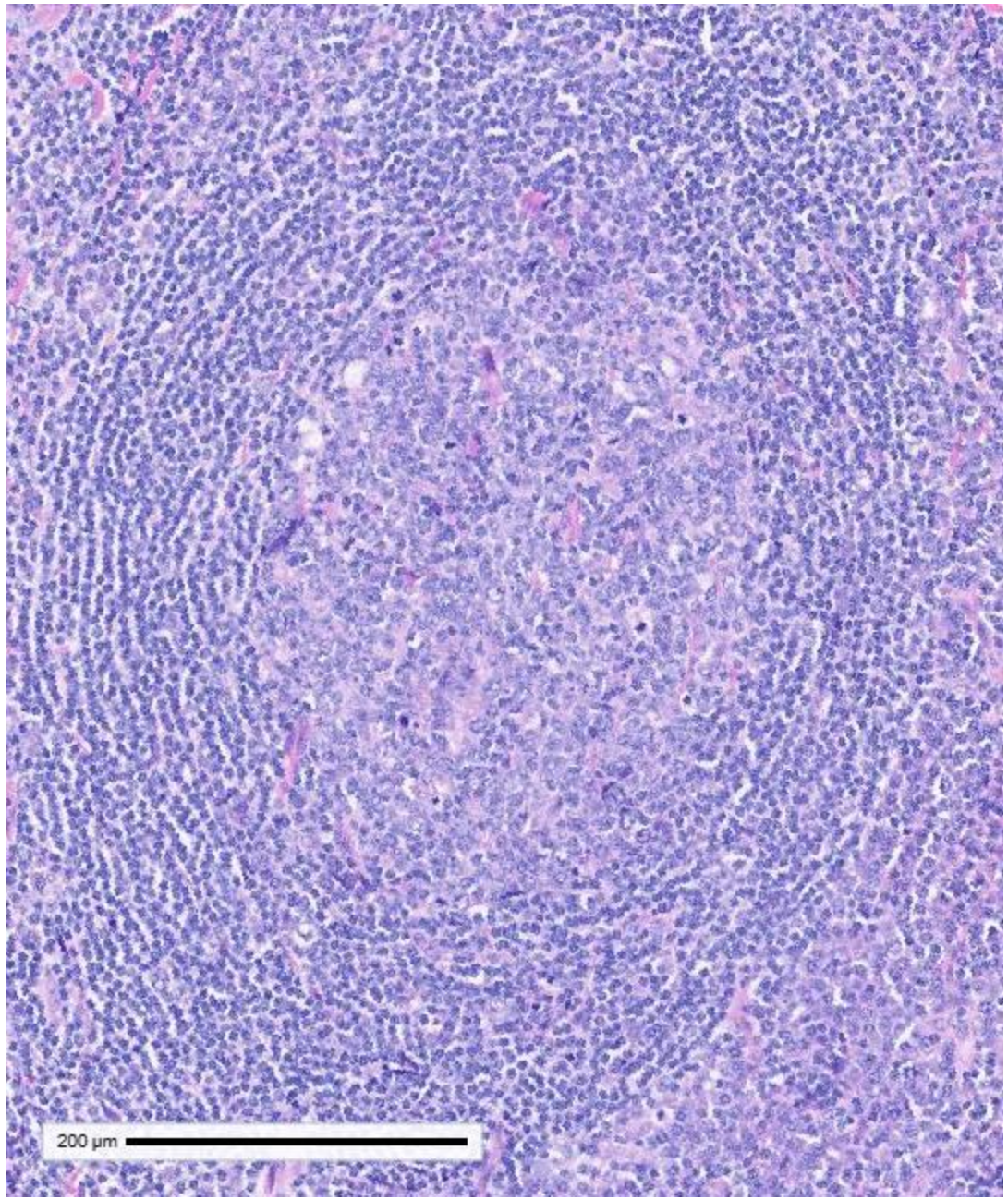
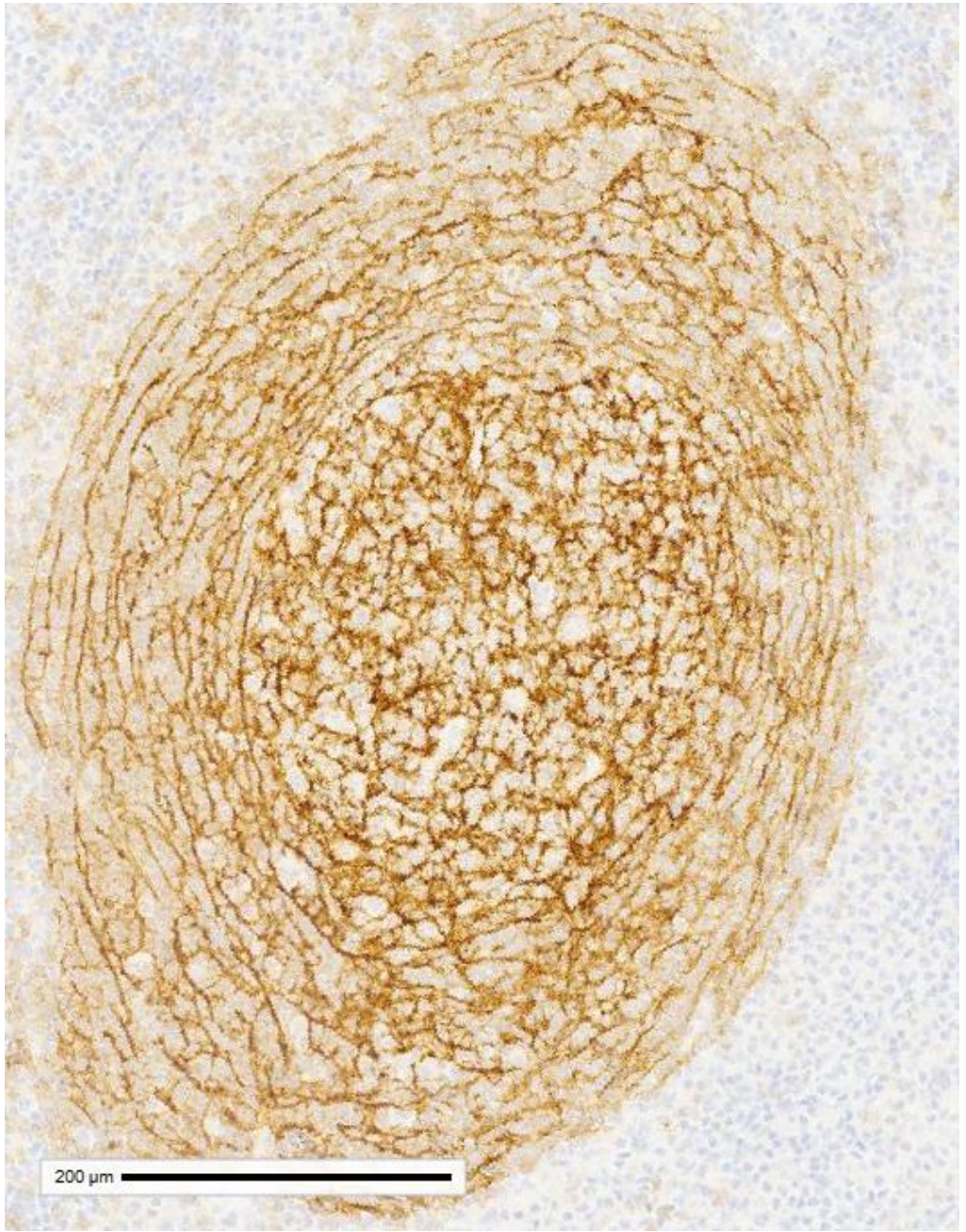
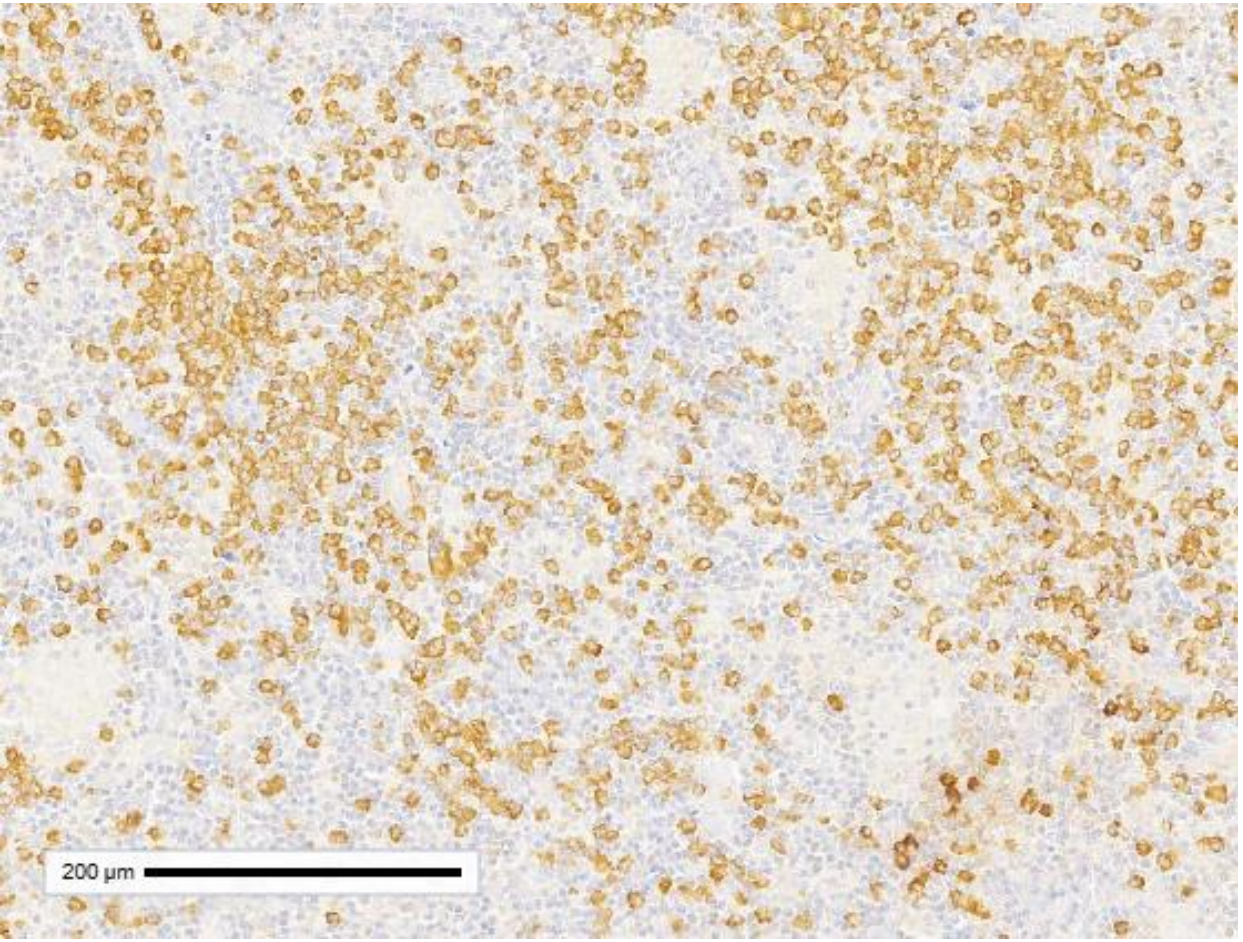
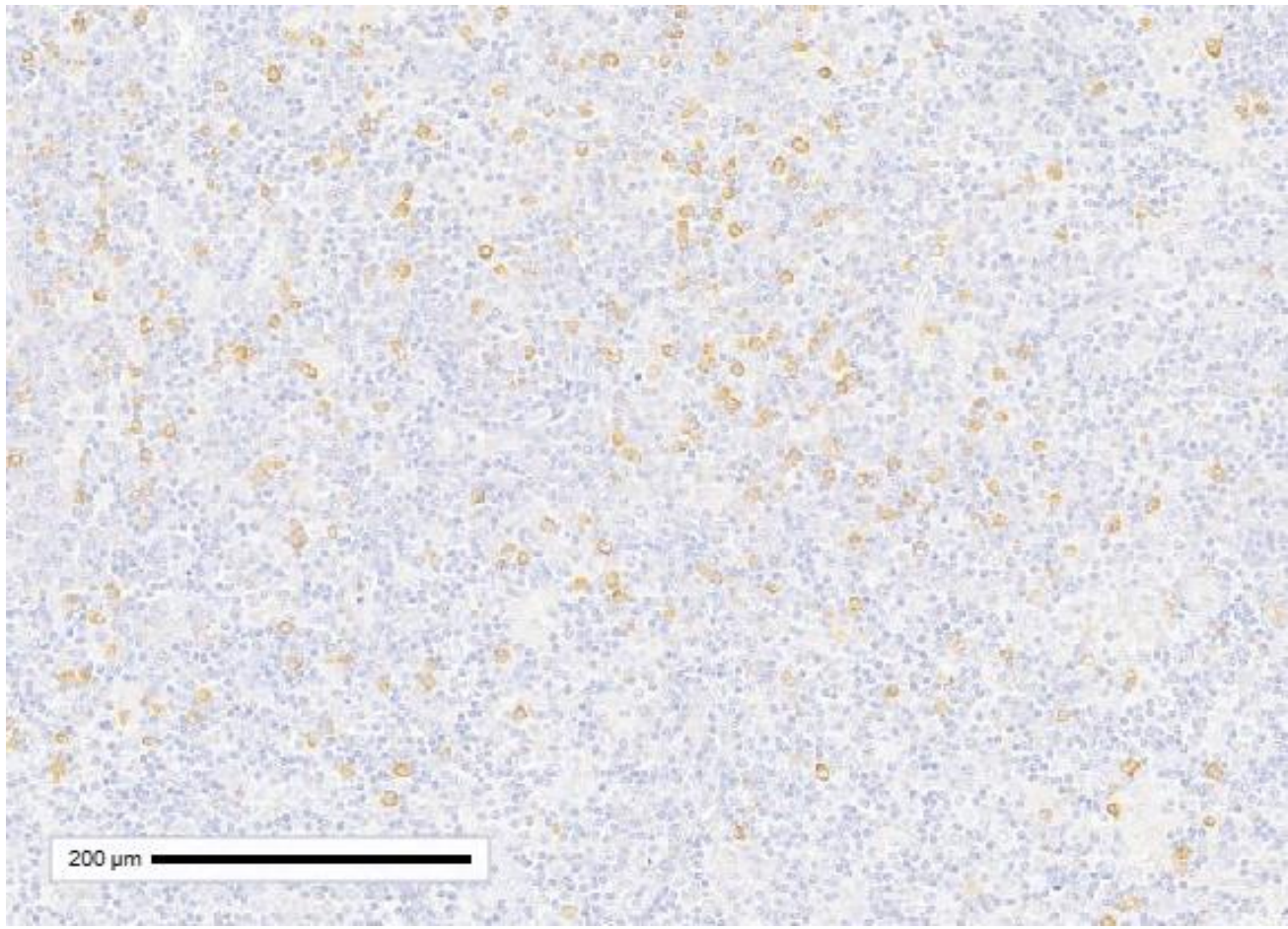




CD21



Kappa-ISH



Lambda-ISH

HHV-8-negative “Idiopathic” Multicentric Castleman Disease (iMCD)

- **Multiple regions of enlarged LNs**
- **Unknown cause drives cytokine release, notably IL-6**
- **Causes flu-like symptoms and multiple organ system impairment**
- **Unknown pathologic cell**
- **Siltuximab and chemotherapy can be effective; relapses common**
- **65% 5-year survival**

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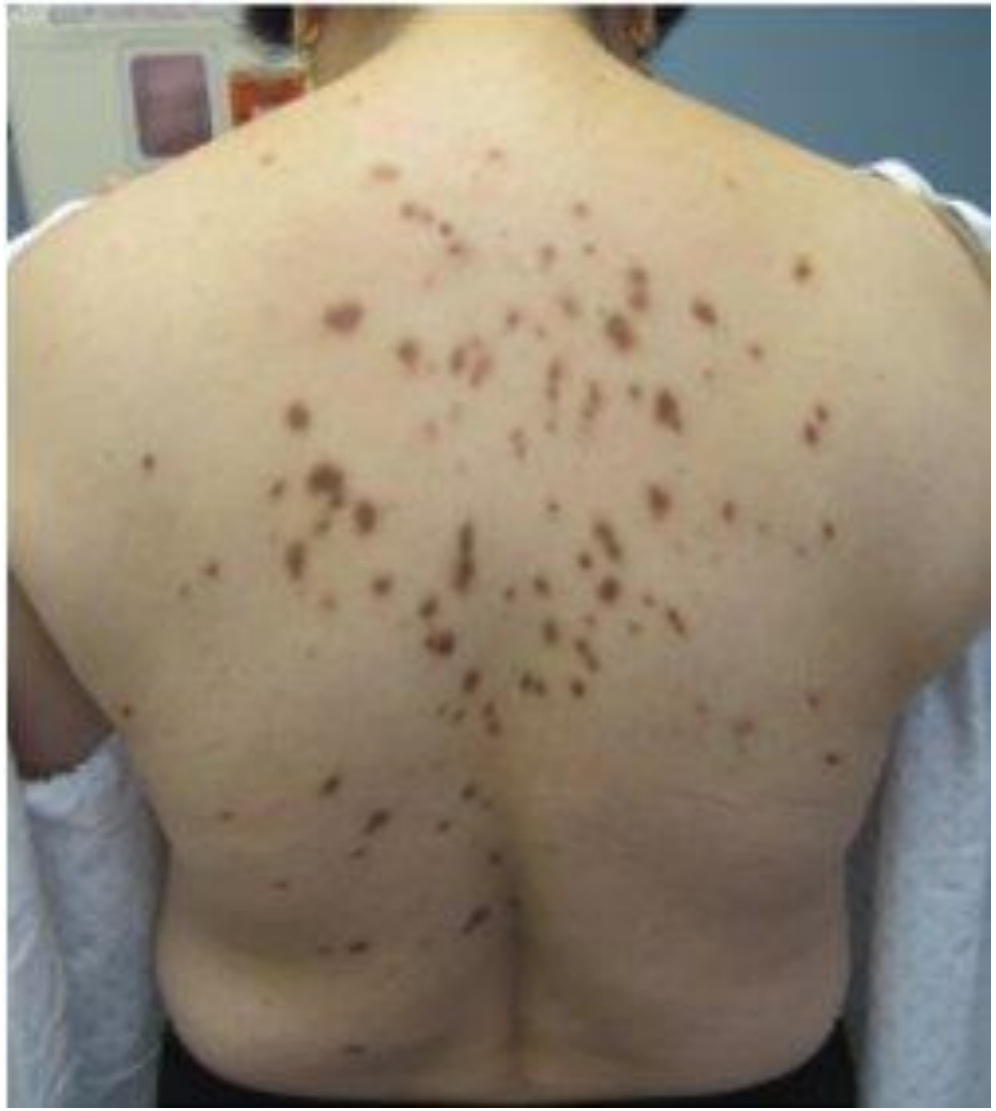
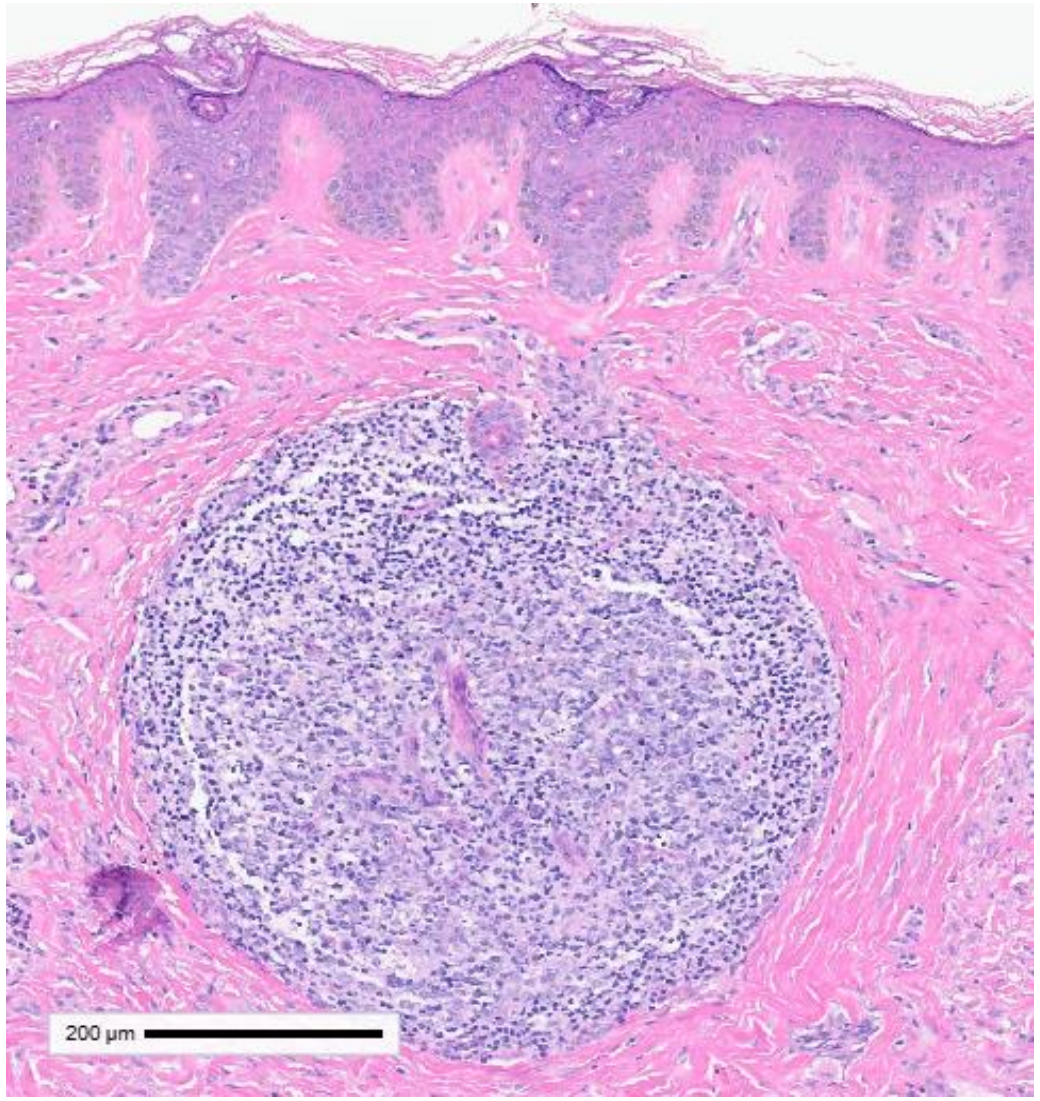
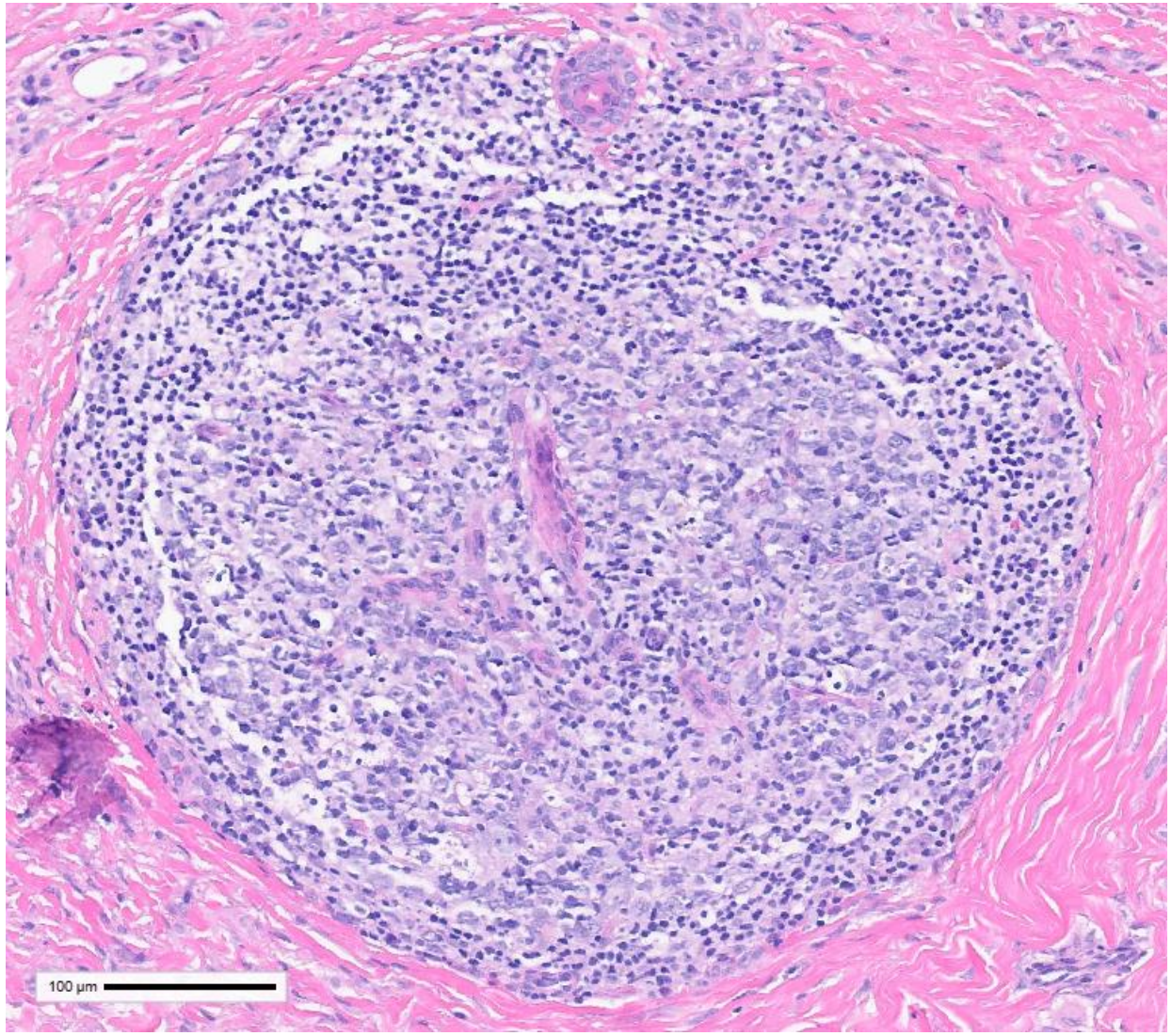
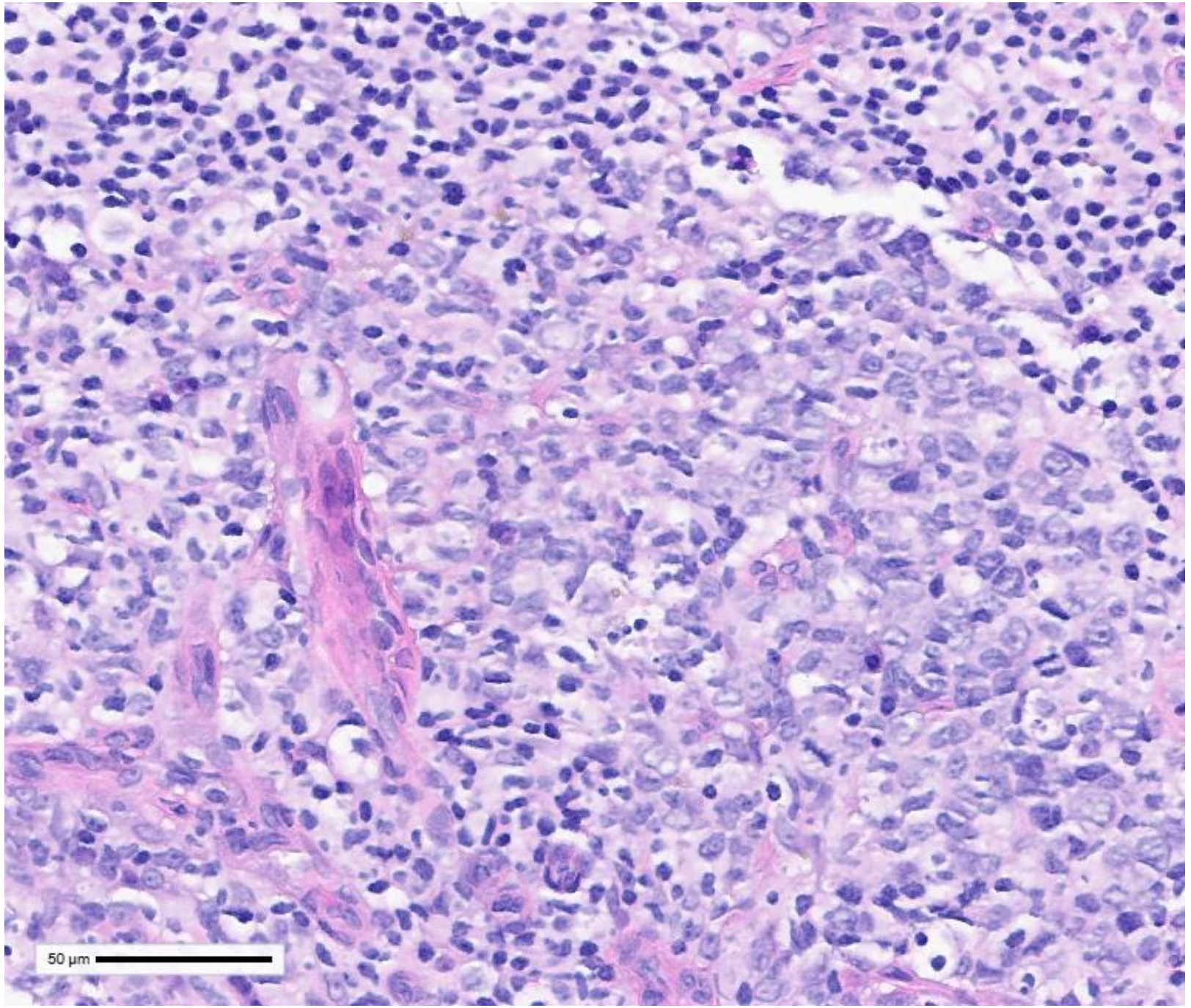
Multicentric Castleman Disease



Multicentric Castleman Disease



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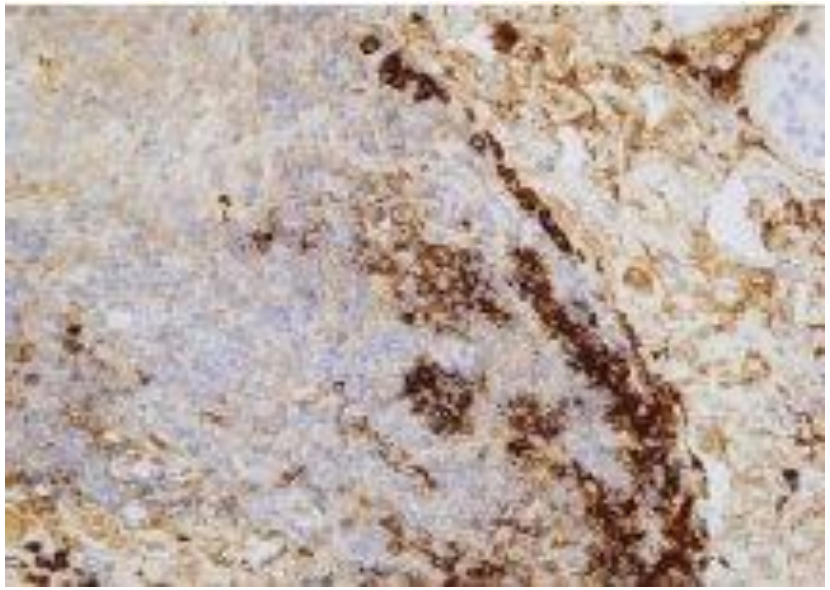

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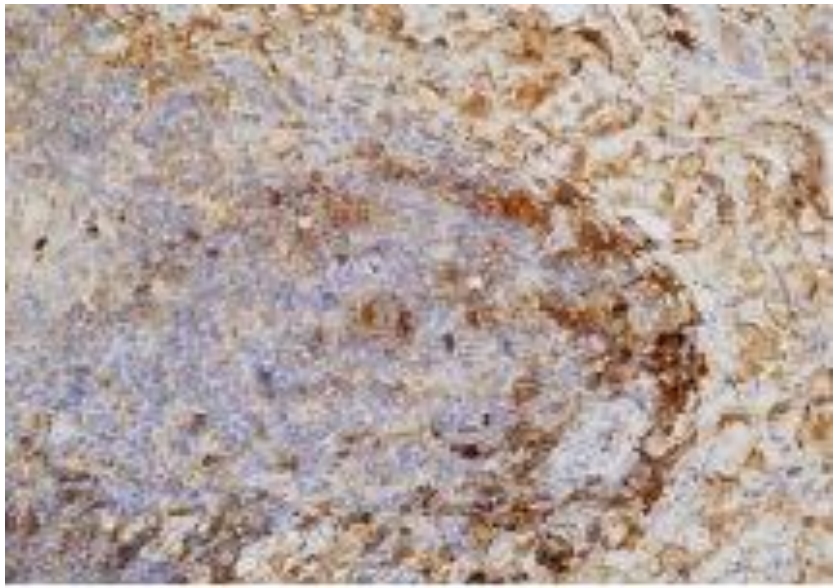

Kappa-ISH

HHV-8-associated Multicentric Castleman Disease (HHV8+MCD)

- Multiple regions of enlarged LNs
- In immunosuppressed, Human Herpes Virus-8 (HHV-8) drives cytokine release, notably IL-6
- Causes flu-like symptoms and multiple organ system impairment (renal failure, pancytopenia, fluid gain)
- HHV-8 lives in B-cells
- B-cell elimination with or without antivirals are effective

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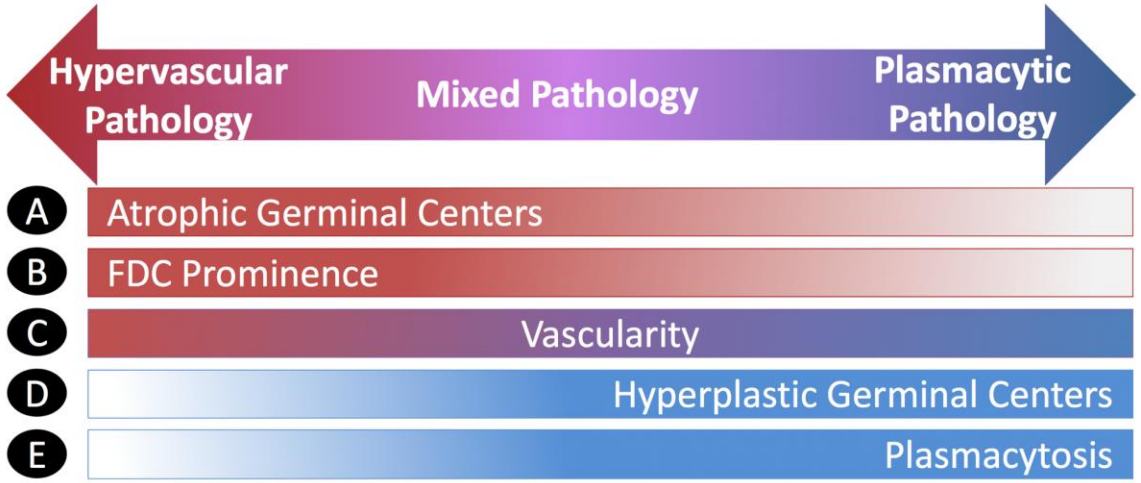
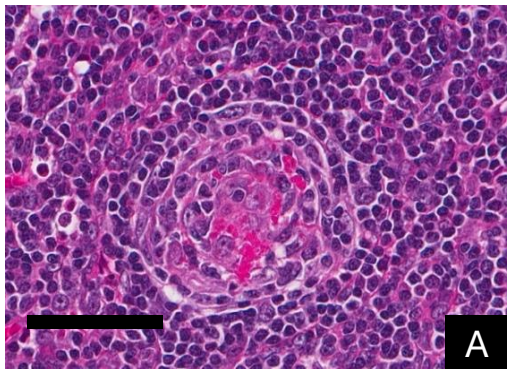
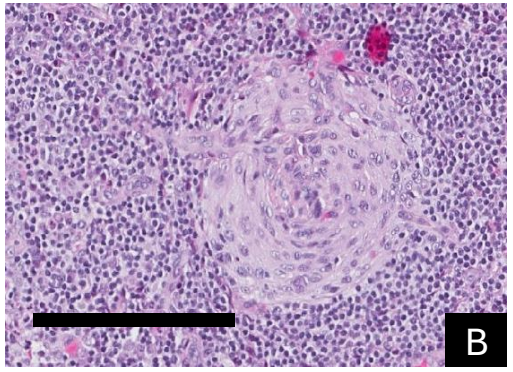
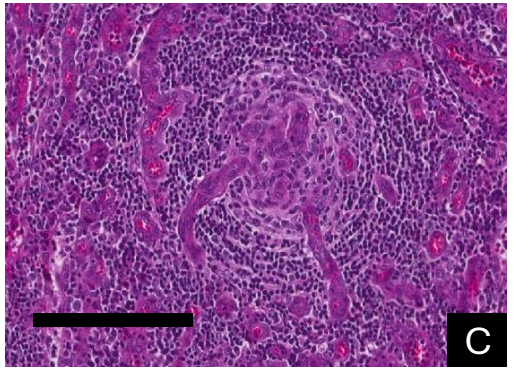
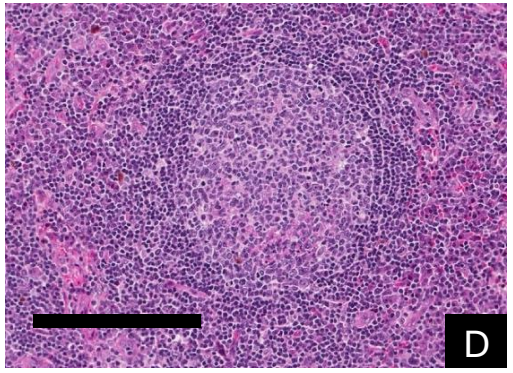
Pathological features across the spectrum

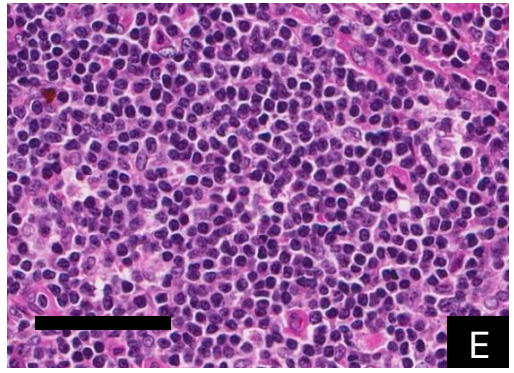






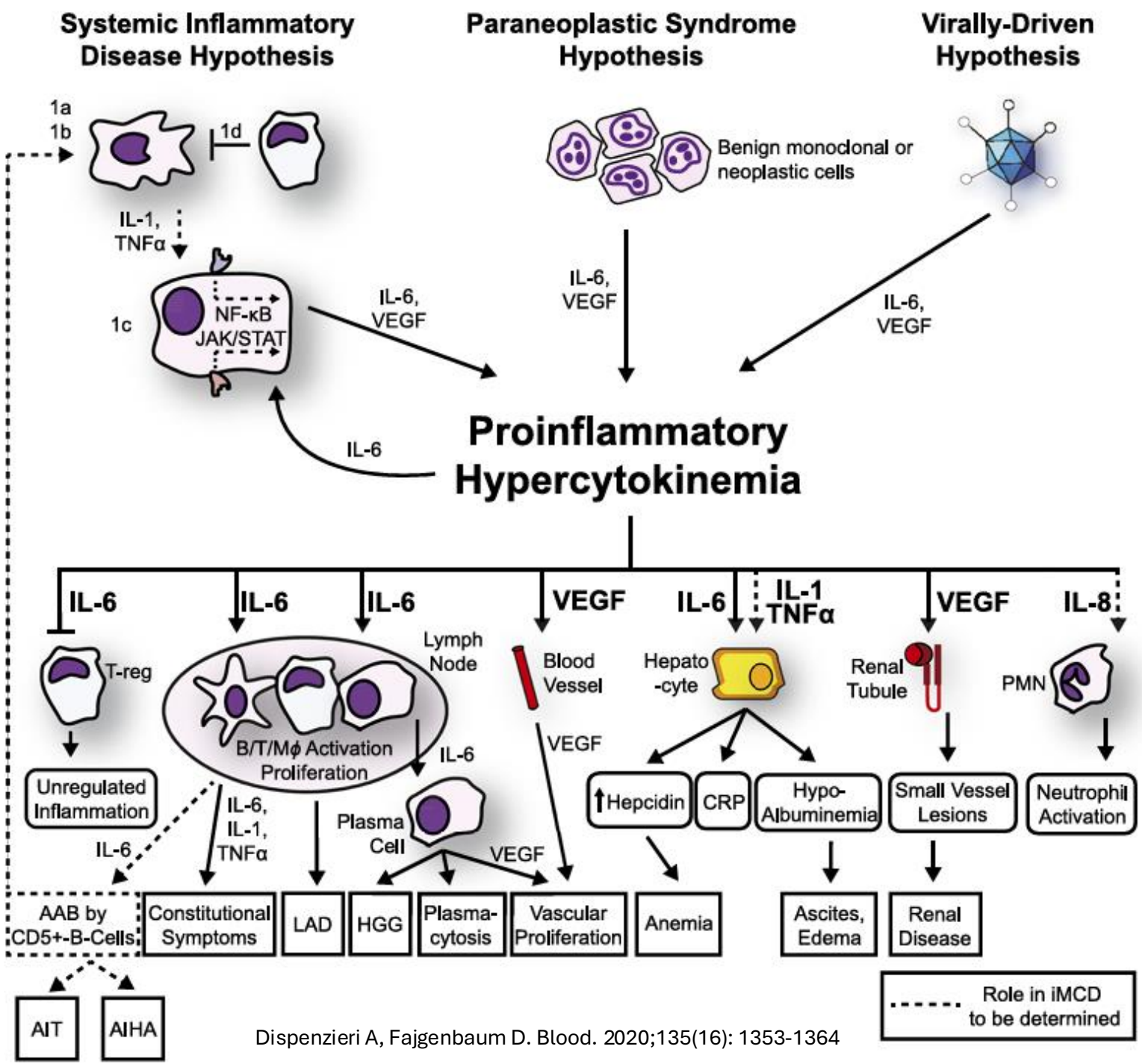






IL-6: A Key Driver in Castleman Disease

- **IL-6 first described in 1973 by Kishimoto et al as a soluble factor excreted by T-cells was important for antibody production by B-cells**
- **IL-6 is a cytokine featuring pleiotropic activity; it induces synthesis of acute phase proteins such as CRP, serum amyloid A, fibrinogen**
- **IL-6 also plays an important role on acquired immune response by stimulation of antibody production and of effector T-cell development. Moreover, IL-6 can promote differentiation or proliferation of several nonimmune cells.**
- **Because of pleiotropic activity, dysregulated continual production of IL-6 leads to onset or development of various diseases.**



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Acknowledgements

- **Cynthia Magro, MD**
- **Petro Vavrukh, MD**

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