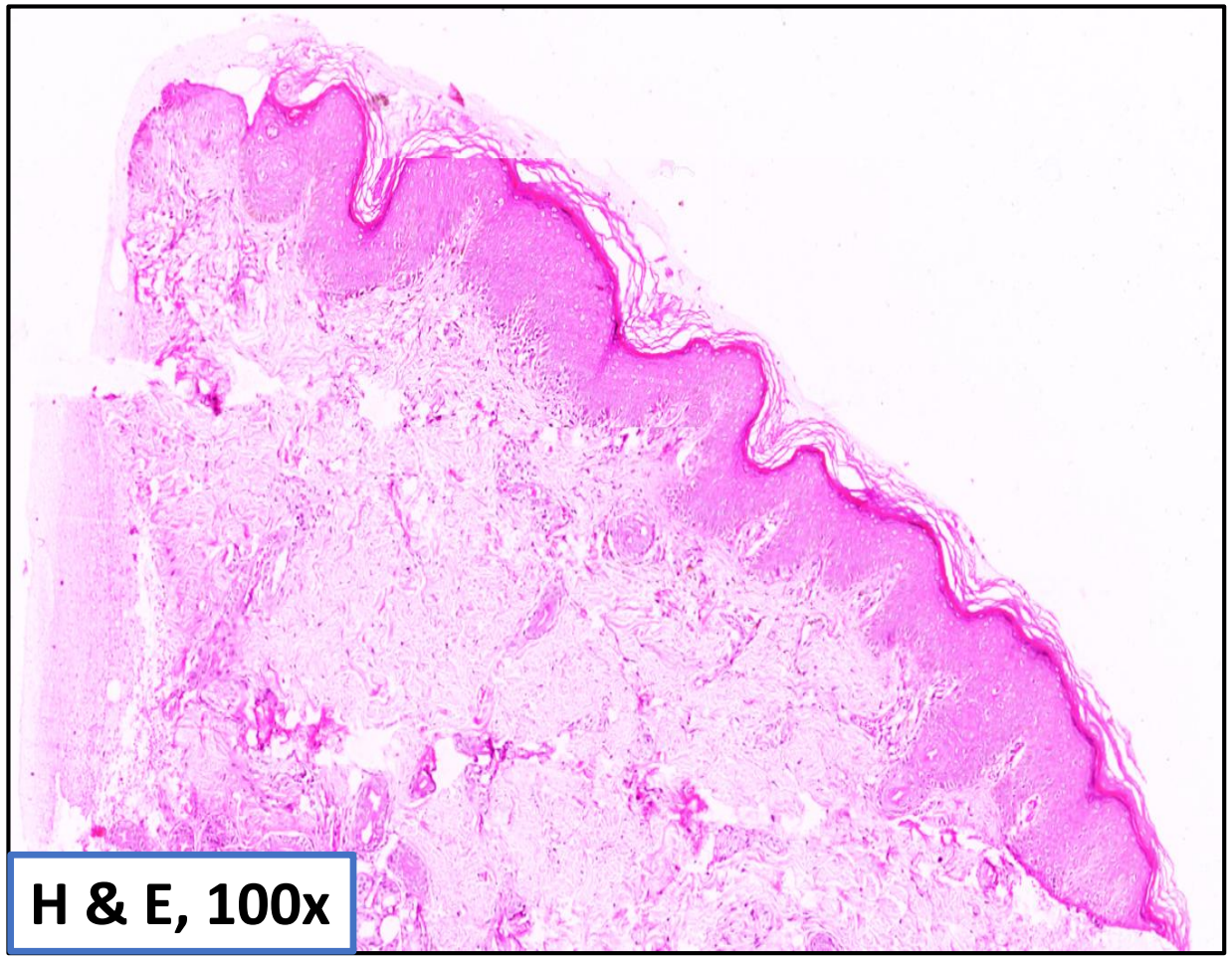
History

- 41 yr old male presented with complaints of multiple painful erosions, involving oral cavity, lips, genital mucosa and hands since 06 months
- Associated with significant weight loss of 17 kg over 06 months.
- Dermatological examination:
  - Lips – Multiple coalescing erosions with hemorrhagic crusting
  - Buccal mucosa, tongue, hard palate & hands – Multiple ill-defined polysized erosions

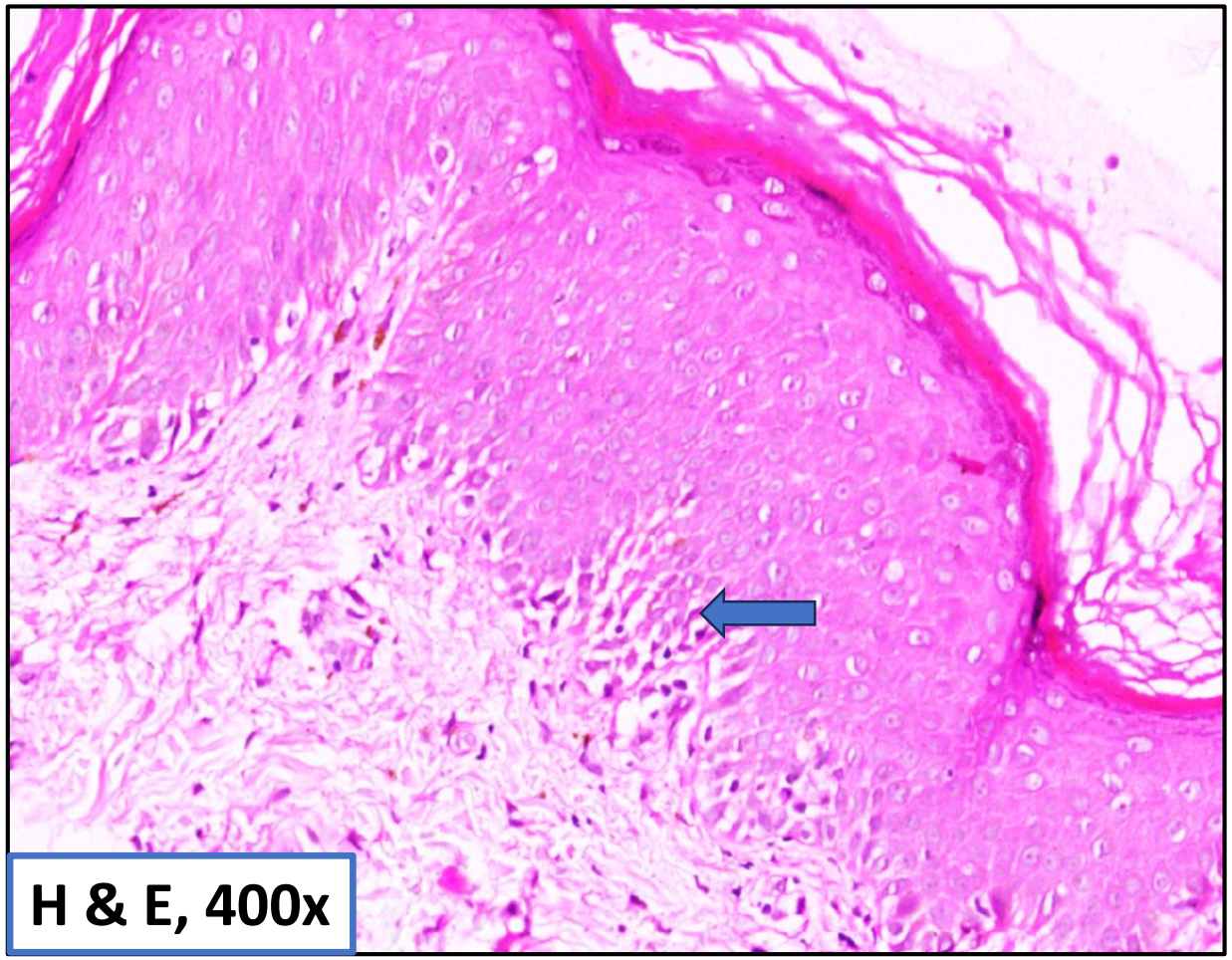
Differential diagnosis

- Erosive Lichen Planus
- Mucous membrane Pemphigoid
- Lichen Planus Pemphigoides
- Lichenoid Drug reaction
- Paraneoplastic Pemphigus
- Erythema Multiforme

Skin biopsy from lesion over hand



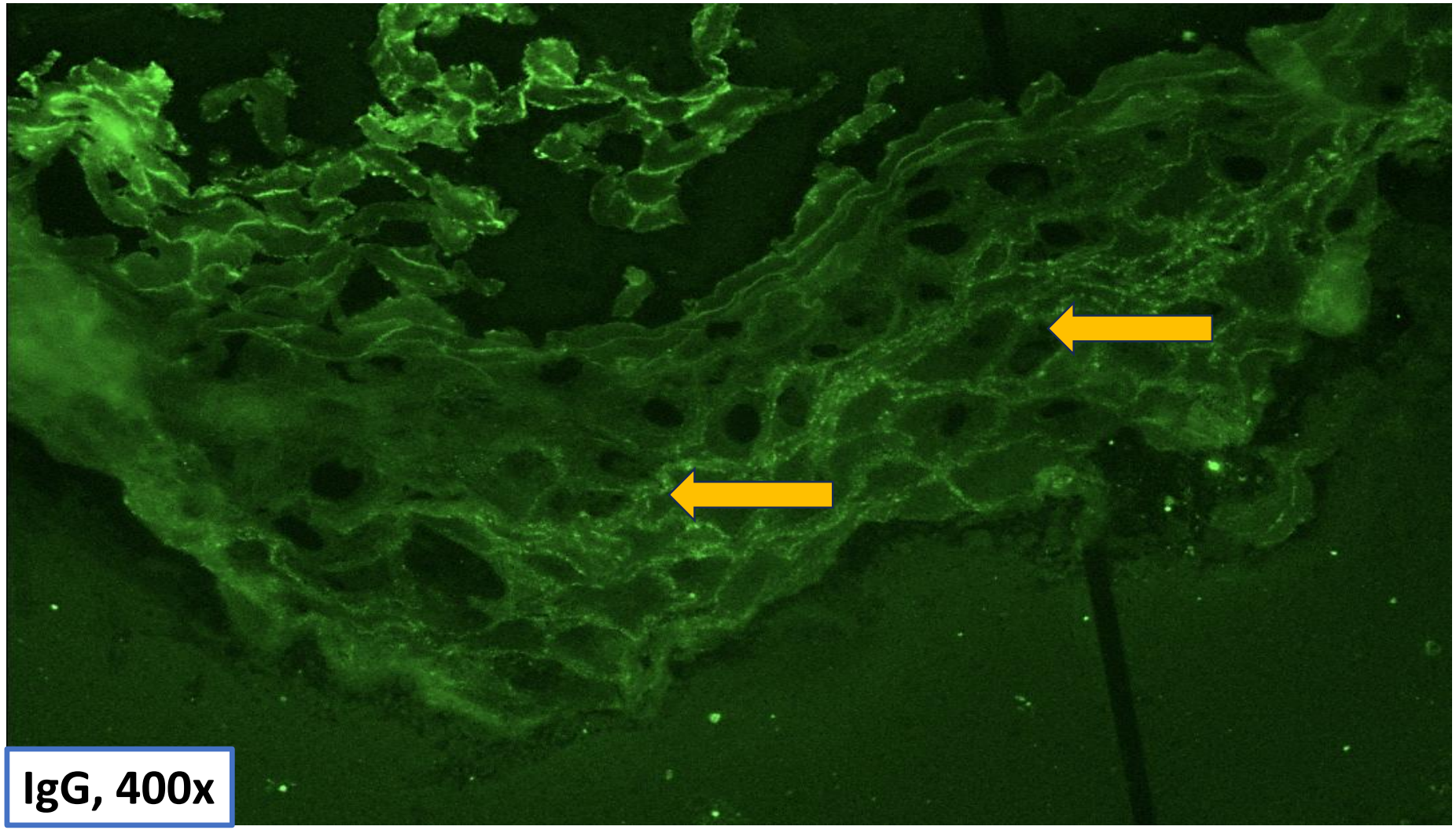
H & E, 100x



H & E, 400x

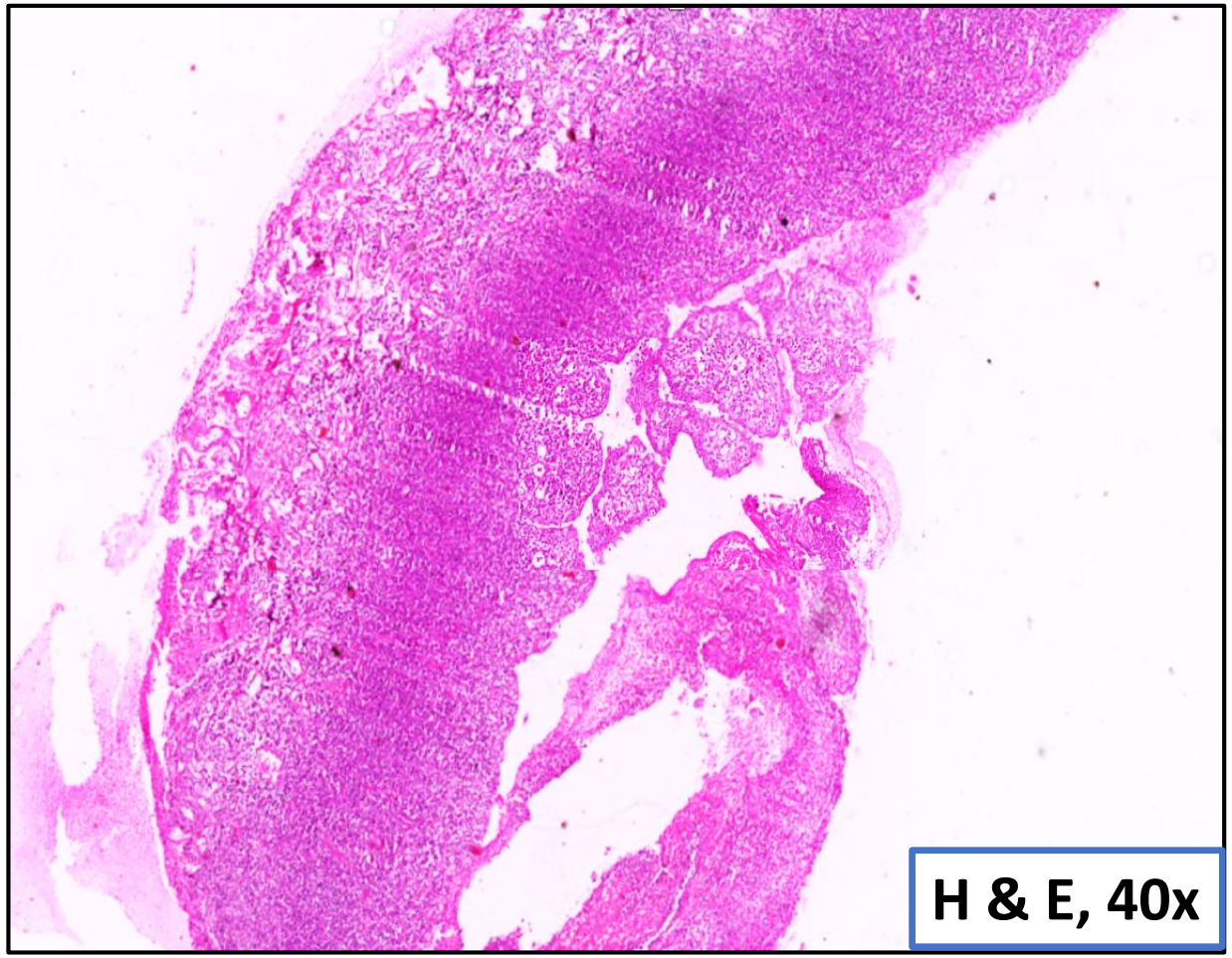
Focal spongiosis

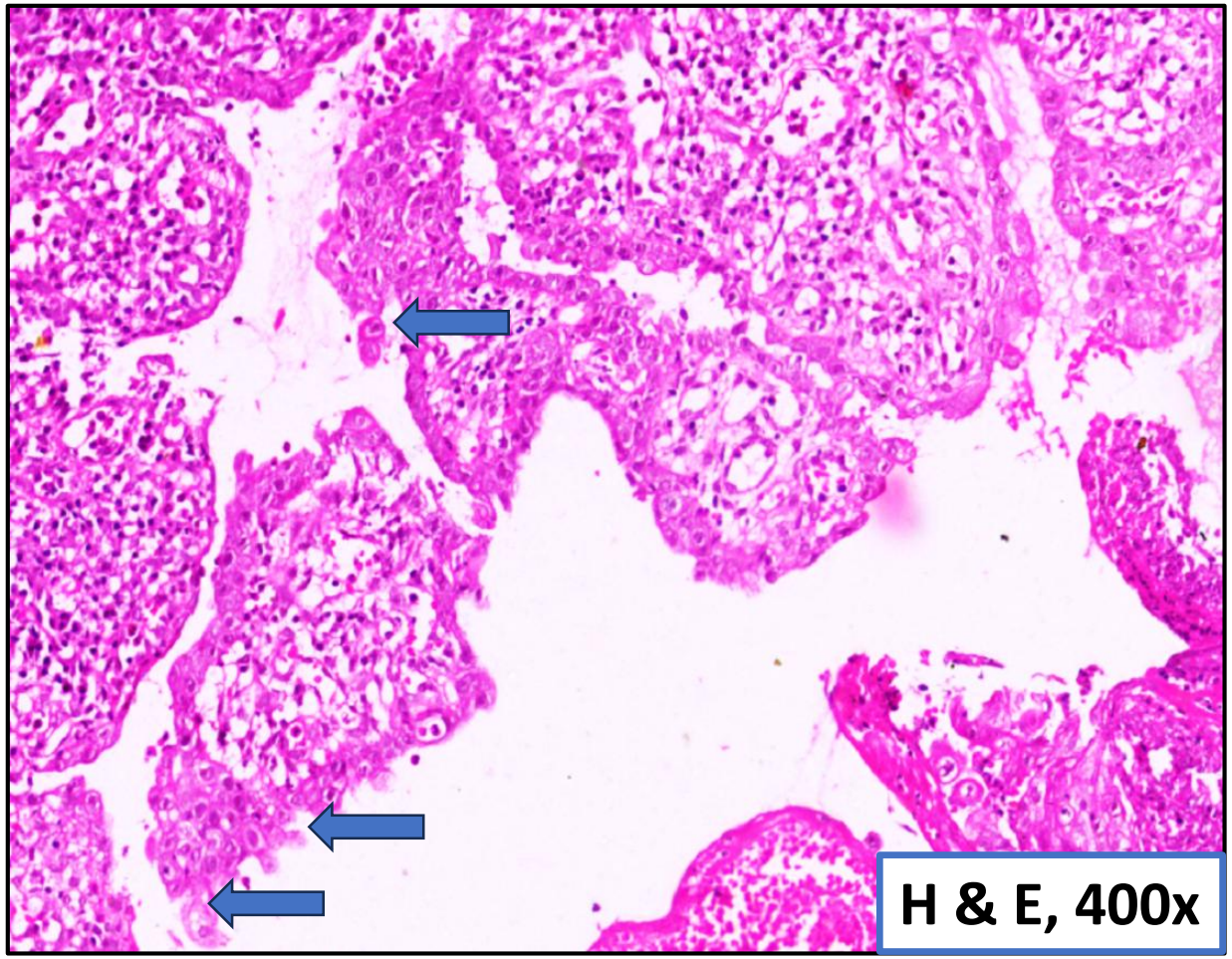
DIF on skin biopsy from lesion over hand



Intraepidermal fishnet pattern of IgG deposition. No linear IgG deposition at dermo-epidermal junction

Biopsy from lesion over lip





Focal acantholysis with tombstone appearance of basal keratinocytes

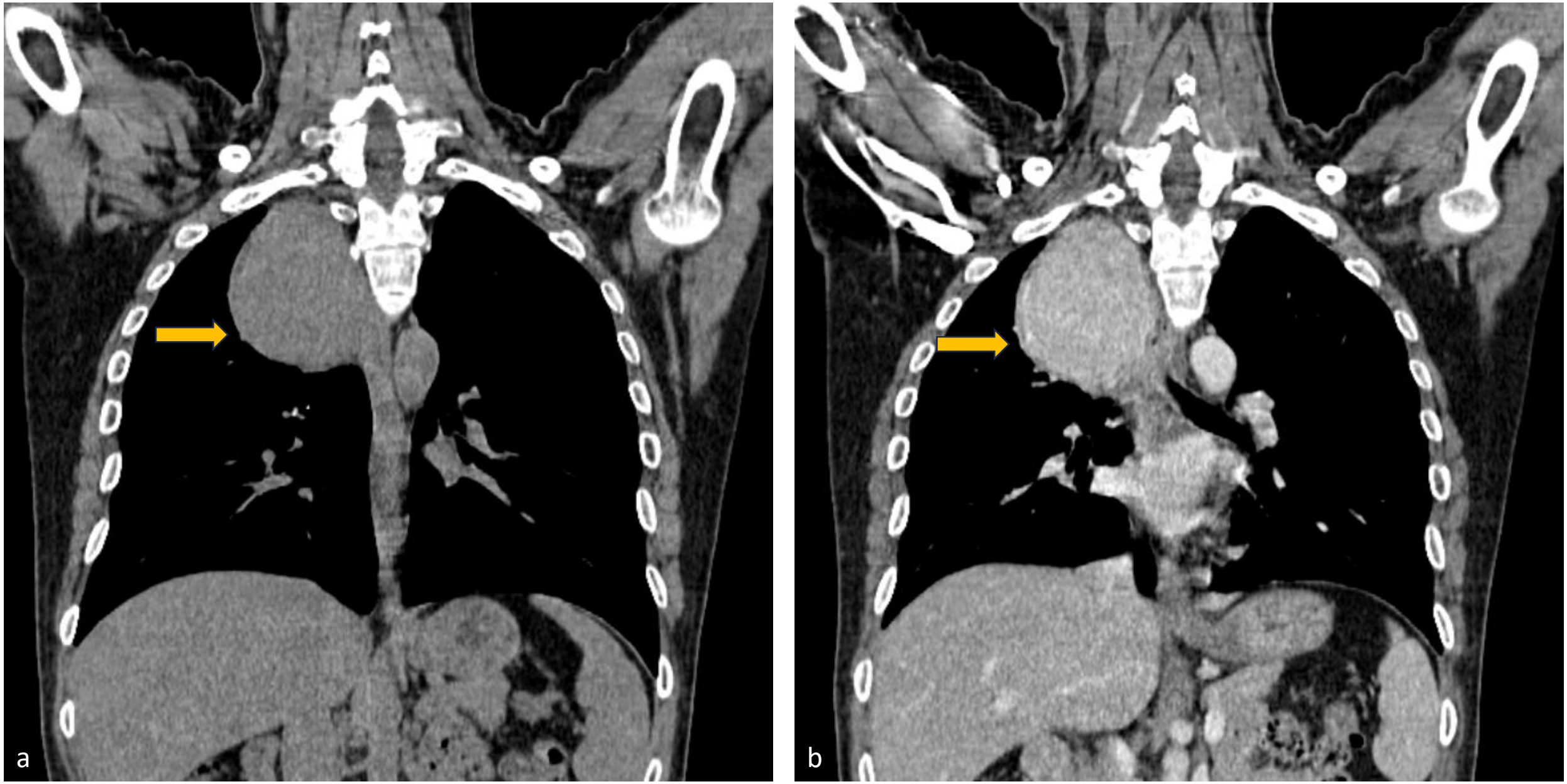
Salient microscopy findings on Skin biopsy

- Skin biopsy from lesion over hand – Spongiosis
- Lip biopsy - Focal acantholysis with row of tombstone appearance of basal keratinocytes
- **DIF:** Intraepidermal fishnet pattern of IgG. No linear IgG deposits

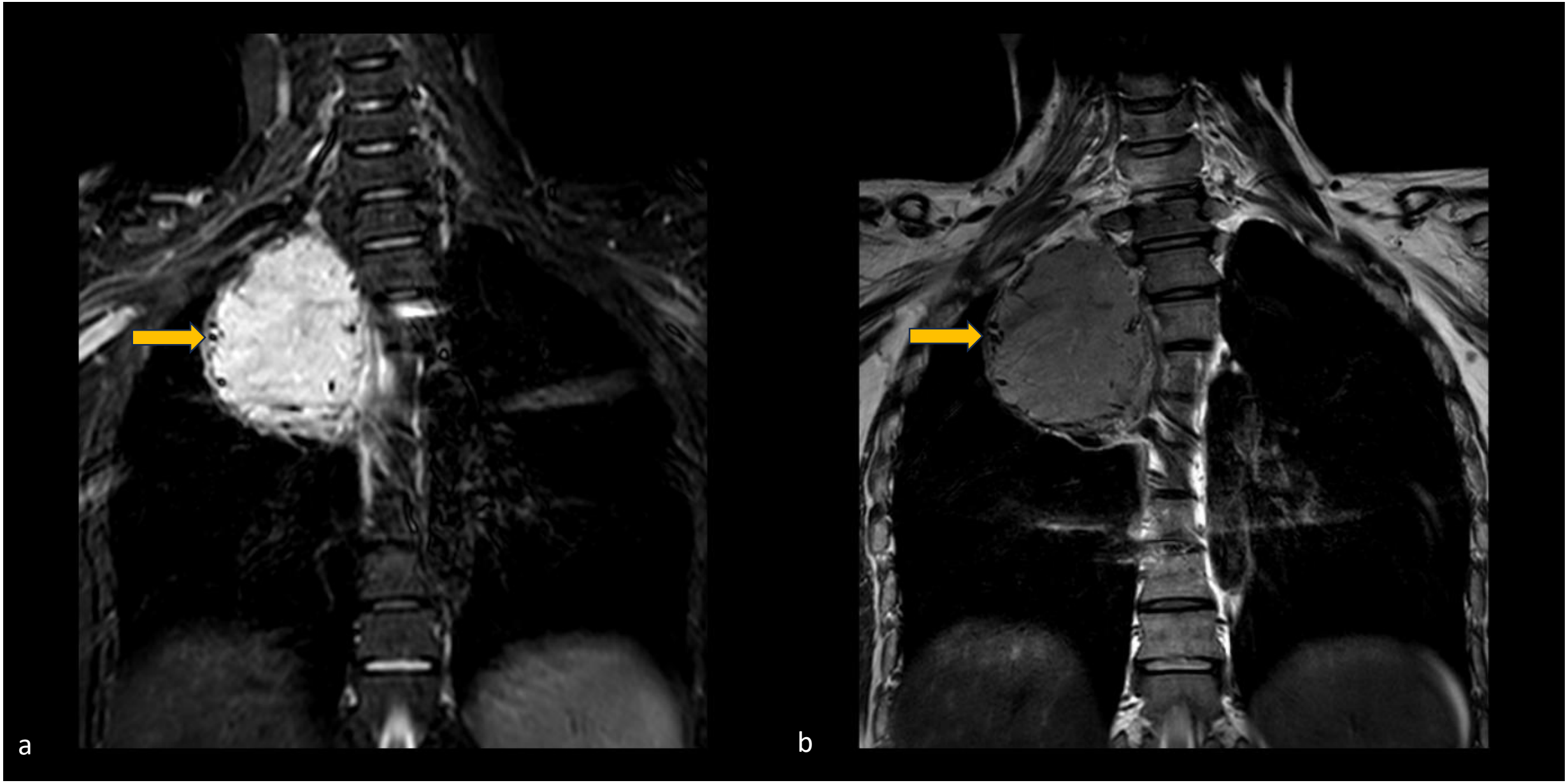
- **Impression:** Overall features suggestive of Pemphigus group of disorders

- Systemic examination did not reveal any significant findings or lymphadenopathy

- In view of significant weight loss, NCCT, CECT & CE MRI performed



Coronal NCCT (a) & CECT (b) – Well defined, avidly enhancing right posterior mediastinal mass



Coronal STIR (a) & T2-weighted (b) MR – Well-circumscribed, hyperintense posterior mediastinal masss

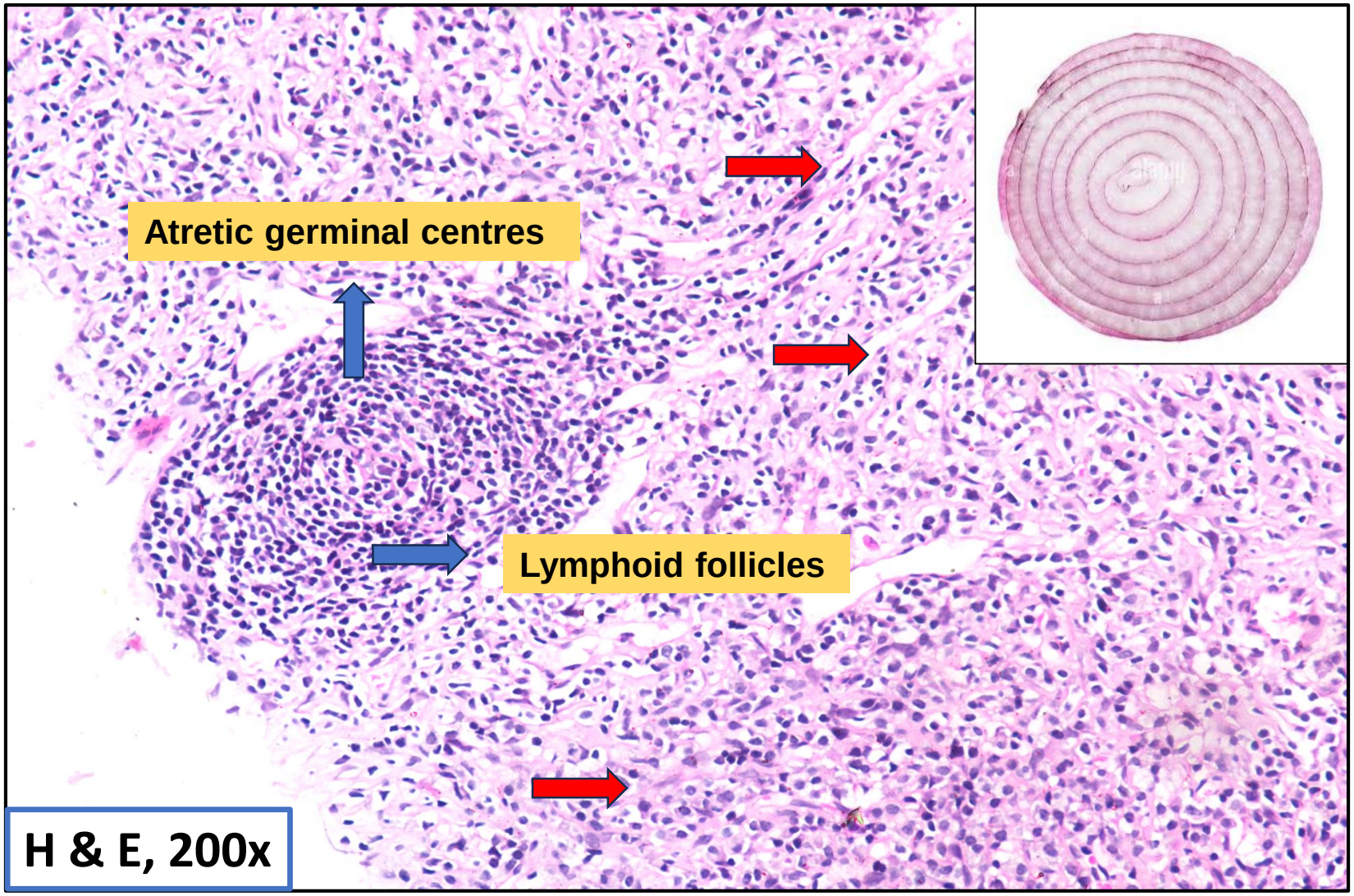
Coronal NCCT & CECT

- Well-defined avidly enhancing right posterior mediastinal mass measuring 75 x 63 x 88 mm
- Extending from D1-D5 level
- Avid post-contrast enhancement
- Possibility of Peripheral nerve sheath tumour

Coronal STIR & T2 weighted MRI

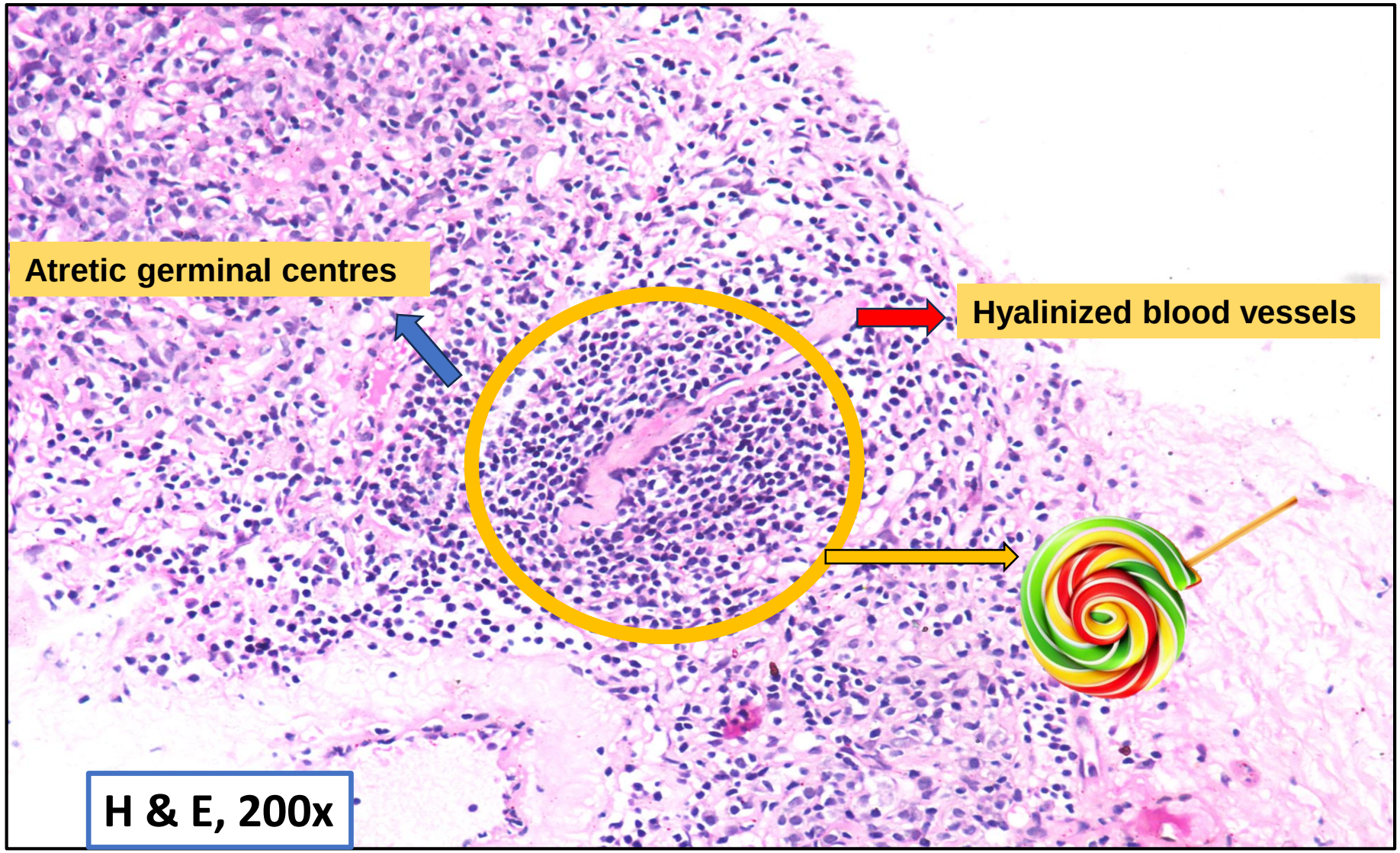
- Well-defined, hyperintense posterior mediastinal mass measuring 71 x 63 x 81 mm
- Multiple peripheral linear flow voids, with few coursing through the lesion, likely vessels.
- D/D: 1. Lymph nodal mass – Unicentric Castlemam disease; 2. Peripheral nerve sheath tumour; 3. Paraganglioma

CT guided biopsy from posterior mediastinal mass



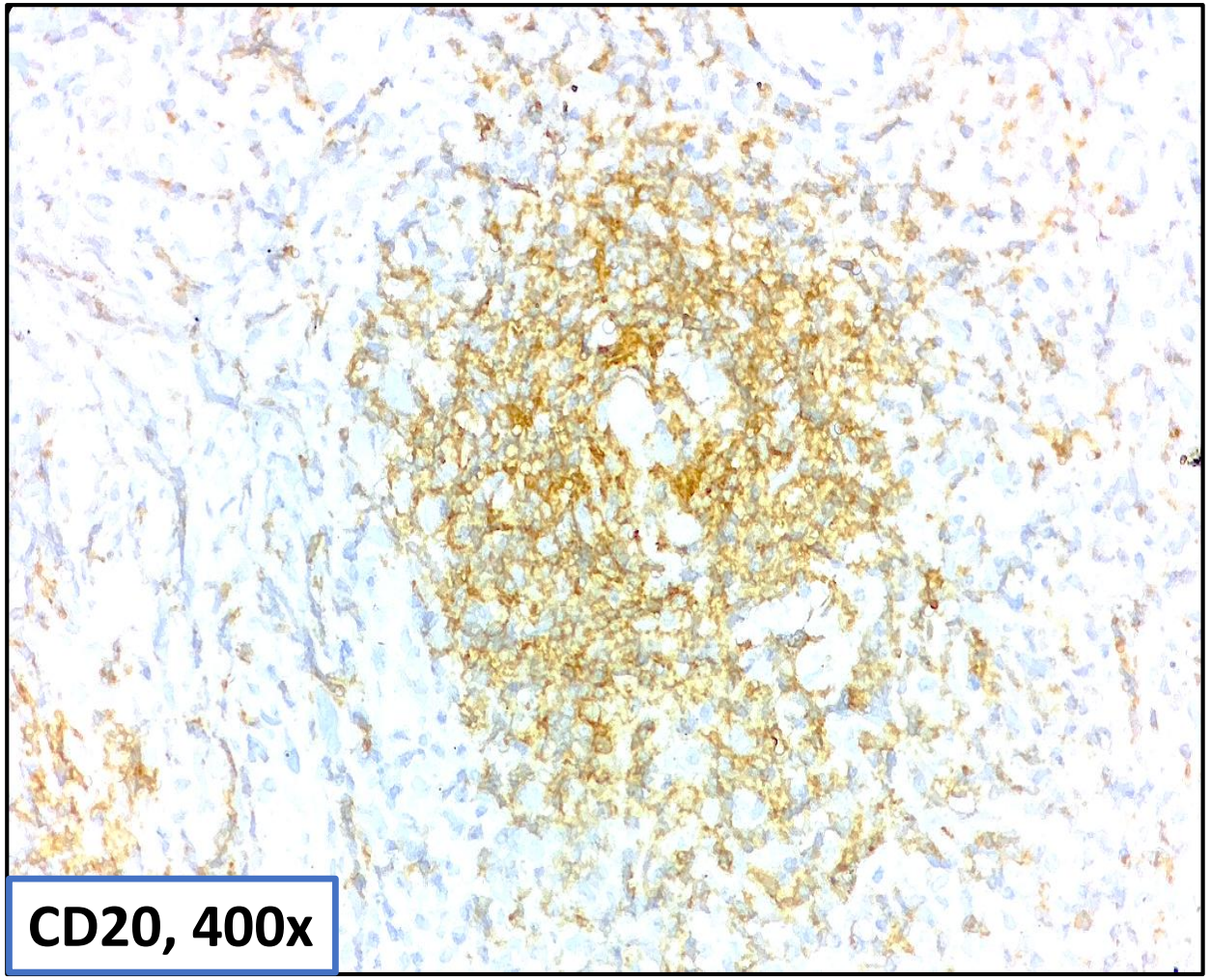
Atretic germinal centres with '*onion skinning*' of Mantle zone. Increased vascularity and occasional plasma cells in interfollicular areas

CT guided biopsy from posterior mediastinal mass

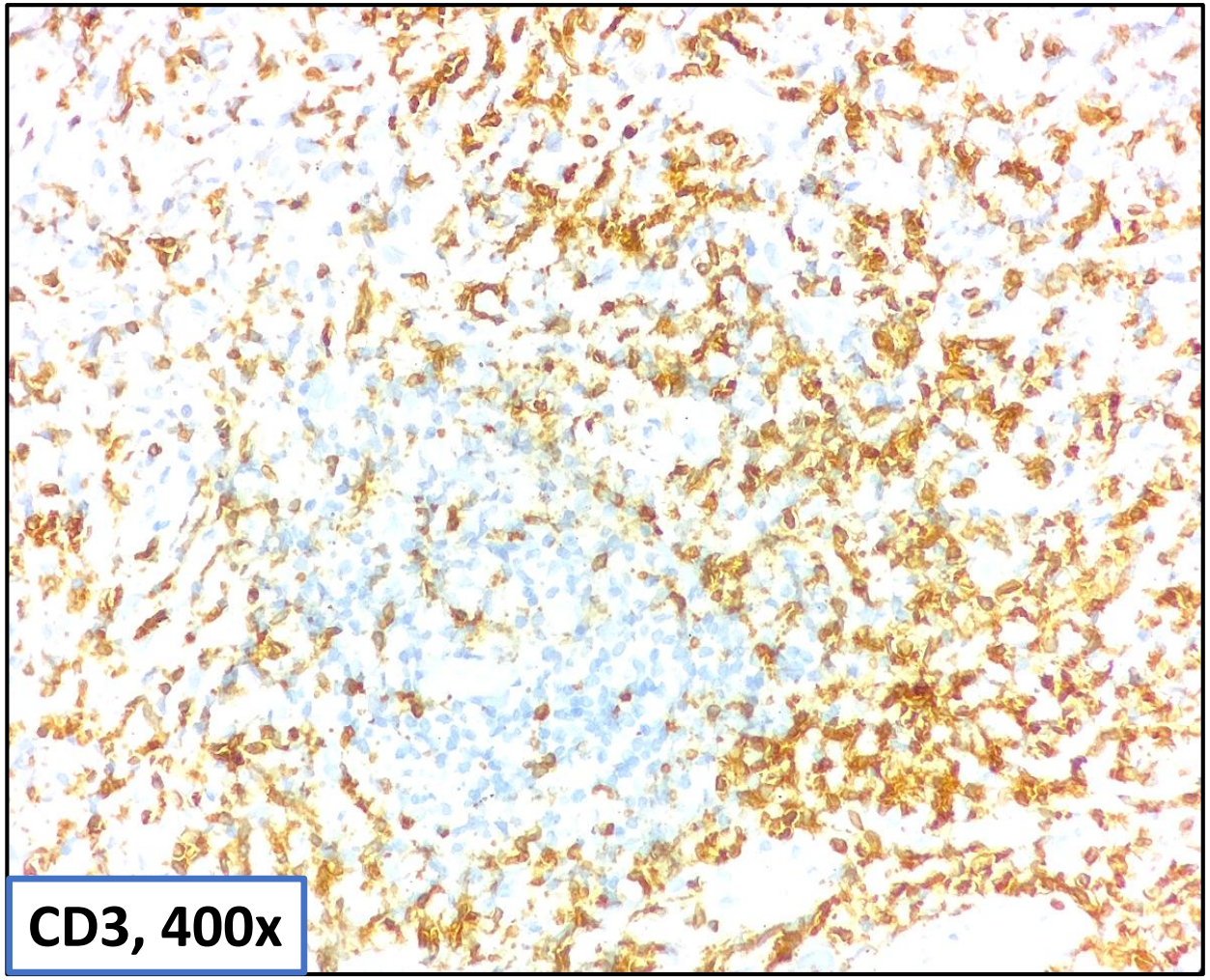


Atretic germinal centres with onion skinning of Mantle zone and hyalinized blood vessels (*Lollipop follicles*)

CT guided biopsy from posterior mediastinal mass



CD20, 400x

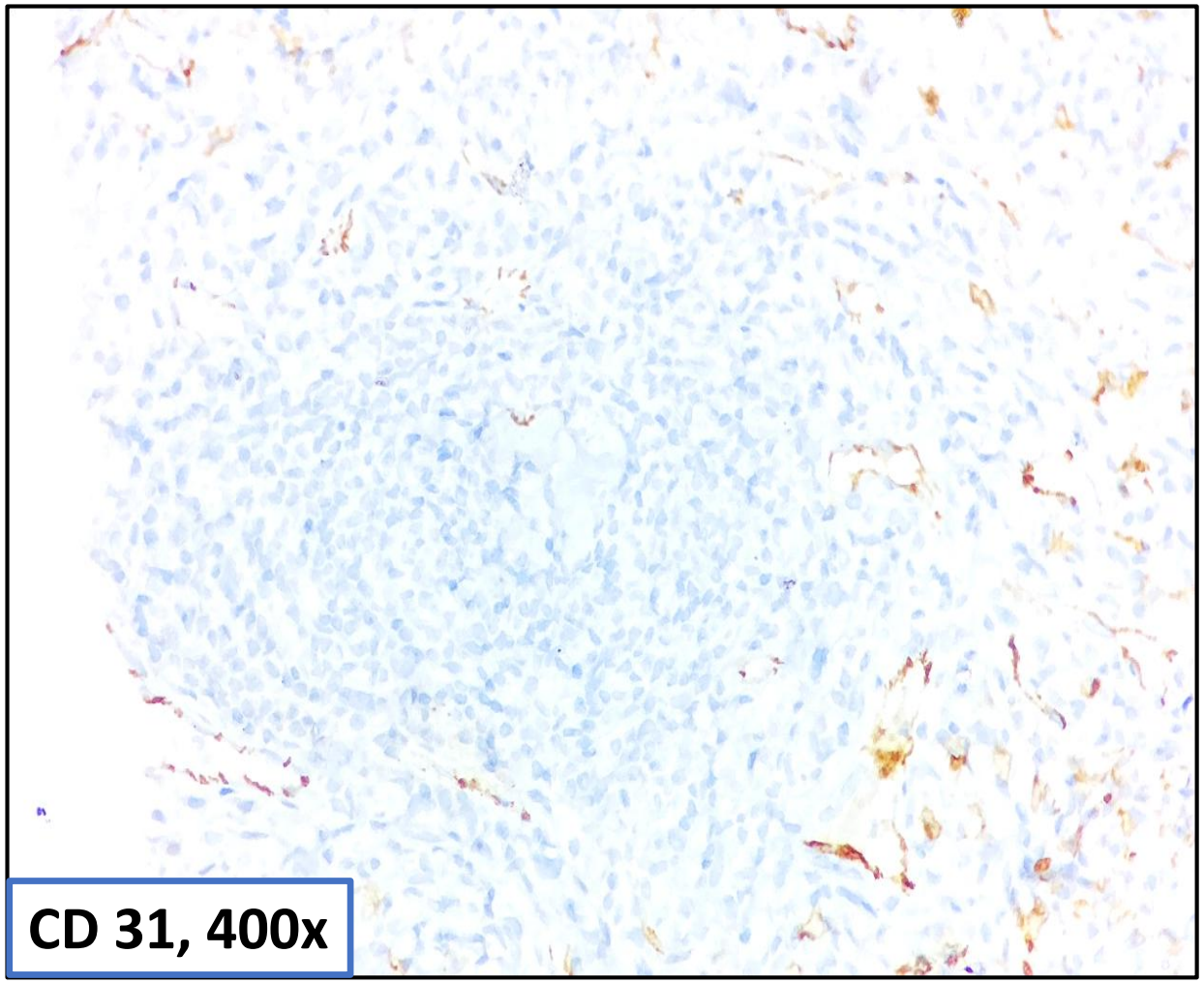


CD3, 400x

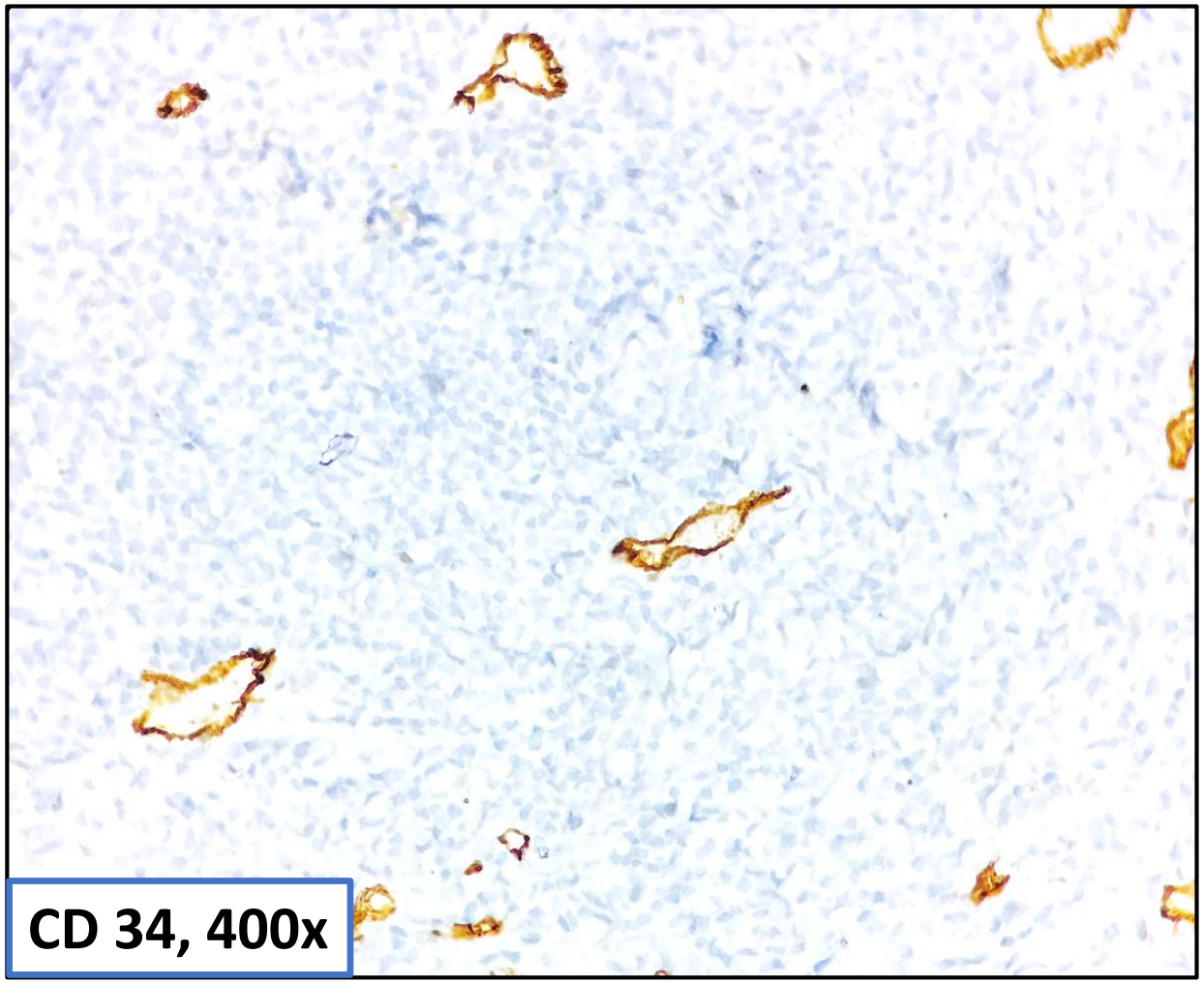
Highlights Reactive germinal centers

Highlights interfollicular areas

CT guided biopsy from posterior mediastinal mass



CD 31, 400x



CD 34, 400x

Highlights blood vessels and increased vascularity in interfollicular areas

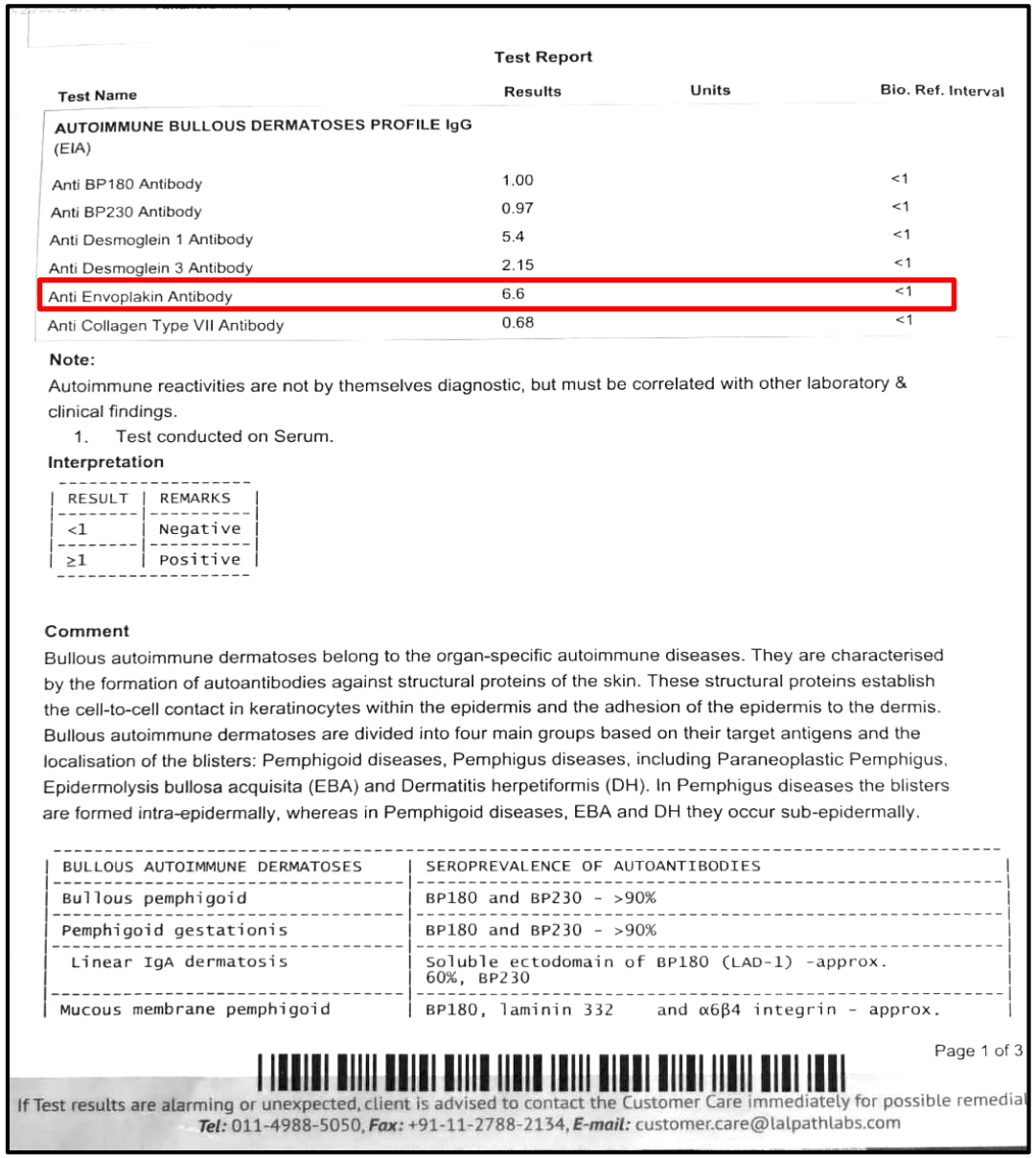
Salient microscopy findings on CT guided biopsy from posterior mediastinal mass

- Tissue cores composed of reactive lymphoid parenchyma with numerous secondary lymphoid follicles
- Atretic germinal centers surrounded by concentrically arranged Mantle zone of small mature lymphocytes – '*Onion skin*' appearance
- Hyalinized blood vessels traversing germinal centres – '*Lollipop follicles'*
- Mild increase in vascularity in interfollicular areas with scattered plasma cells
- No granuloma/features of malignancy or metastatic deposits

Salient microscopy findings on CT guided biopsy from posterior mediastinal mass

- **Immunohistochemistry:**
  - **CD20:** Positive in reactive germinal centers
  - **CD3:** Positive in interfollicular areas
  - **CD31 & CD34:** Highlight blood vessels
  - **Ki67 proliferation index:** 60-65% in reactive germinal centers

Antibody profile



Test Report

Test Name	Results	Units	Bio. Ref. Interval
AUTOIMMUNE BULLOUS DERMATOSES PROFILE IgG (EIA)			
Anti BP180 Antibody	1.00		<1
Anti BP230 Antibody	0.97		<1
Anti Desmoglein 1 Antibody	5.4		<1
Anti Desmoglein 3 Antibody	2.15		<1
Anti Envoplakin Antibody	6.6		<1
Anti Collagen Type VII Antibody	0.68		<1

Note:

Autoimmune reactivities are not by themselves diagnostic, but must be correlated with other laboratory & clinical findings.

1. Test conducted on Serum.

Interpretation

RESULT	REMARKS
<1	Negative
≥1	Positive

Comment

Bullous autoimmune dermatoses belong to the organ-specific autoimmune diseases. They are characterised by the formation of autoantibodies against structural proteins of the skin. These structural proteins establish the cell-to-cell contact in keratinocytes within the epidermis and the adhesion of the epidermis to the dermis. Bullous autoimmune dermatoses are divided into four main groups based on their target antigens and the localisation of the blisters: Pemphigoid diseases, Pemphigus diseases, including Paraneoplastic Pemphigus, Epidermolysis bullosa acquisita (EBA) and Dermatitis herpetiformis (DH). In Pemphigus diseases the blisters are formed intra-epidermally, whereas in Pemphigoid diseases, EBA and DH they occur sub-epidermally.

BULLOUS AUTOIMMUNE DERMATOSES	SEROPREVALENCE OF AUTOANTIBODIES
Bullous pemphigoid	BP180 and BP230 - >90%
Pemphigoid gestationis	BP180 and BP230 - >90%
Linear IgA dermatosis	Soluble ectodomain of BP180 (LAD-1) -approx. 60%, BP230
Mucous membrane pemphigoid	BP180, laminin 332 and α6β4 integrin - approx.

Page 1 of 3

If Test results are alarming or unexpected, client is advised to contact the Customer Care immediately for possible remedial

Tel: 011-4988-5050, *Fax:* +91-11-2788-2134, *E-mail:* customer.care@lalpathlabs.com

Positive for
Anti – Envoplakin Antibody

Final Diagnosis

Castleman disease (Hyaline vascular type) with secondary Paraneoplastic Pemphigus

Castleman Disease

- Morphologically distinct lymph node proliferation of unknown etiology in most cases
- Most common in adults; can also affect children
- Two major clinical categories:
  - Solitary form
  - Multicentric form
- Two major microscopic categories:
  - Hyaline-vascular or angiofollicular type
  - Plasma cell type

Goldblum, J. R., Lamps, L. W., McKenney, J. K., & Myers, J. L. (2017). *Rosai and Ackerman's Surgical Pathology* (11th ed., Vols. 1–2). Elsevier

Castleman Disease

- Clinical presentation:
  - Solitary form:
    - Mass located commonly in the mediastinum
    - Also in neck, lung, axilla, mesentery, broad ligament, retroperitoneum, nasopharynx and meninges
    - Grossly, round, well-circumscribed with a solid gray-cut surface
    - Microscopically, 90% of cases are of hyaline-vascular type

Goldblum, J. R., Lamps, L. W., McKenney, J. K., & Myers, J. L. (2017). *Rosai and Ackerman's Surgical Pathology* (11th ed., Vols. 1–2). Elsevier

Castleman Disease

- Clinical presentation:
  - Multicentric or systemic form:
    - Generalized lymphadenopathy. May also involve the spleen
    - Etiology unknown. Two main hypotheses – Abnormal immune response and viral infection (HHV8)
    - Sometimes seen in association with POEMS syndrome
    - Microscopically, nearly always Plasma cell type
    - Paraneoplastic Pemphigus and Myasthenia Gravis may be associated with Multicentric disease

Dinesha, Padyana M, Nayak K, Nirupama M, Pai DS. Castleman's Disease with Paraneoplastic Pemphigus. Indian J Dermatol. 2014 Jul;59(4):421

Hyaline-vascular or angiofollicular type

- Large follicles scattered in a mass of lymphoid tissue
- Follicles show marked vascular proliferation and hyalinization of abnormal germinal centers
- Tight concentric layering of lymphocytes at the periphery of follicles (corresponding to mantle zone) – Onion skin appearance
- Interfollicular stroma prominent with numerous hyperplastic vessels of postcapillary venule type, admixture of plasma cells, eosinophils, immunoblasts, CD123-positive plasmacytoid dendritic cells & admixed TdT-positive T cells

Goldblum, J. R., Lamps, L. W., McKenney, J. K., & Myers, J. L. (2017). *Rosai and Ackerman's Surgical Pathology* (11th ed., Vols. 1–2). Elsevier

Plasma cell type

- Characterized by diffuse plasma cell proliferation in interfollicular tissue
- Sometimes accompanied by numerous Russel bodies
- Deposition of amorphous acidophilic material containing fibrin and immune complexes in the center of follicles

Goldblum, J. R., Lamps, L. W., McKenney, J. K., & Myers, J. L. (2017). *Rosai and Ackerman's Surgical Pathology* (11th ed., Vols. 1–2). Elsevier

Castleman Disease

- Long term prognosis of systemic disease is poor
- Persists for months or years
- Results in pulmonary or renal complications
- Sometimes, associated with Kaposi sarcoma
- Other cases have developed large cell lymphomas with plasmablastic features, most associated with HHV8 infection
- Follicular dendritic cell tumours can develop in Hyaline vascular type with atypical follicular dendritic cells and cytogenetic abnormalities
- Also seen in Hyaline vascular type are angiomyoid proliferative lesions and angiomatous hamartomas

Goldblum, J. R., Lamps, L. W., McKenney, J. K., & Myers, J. L. (2017). *Rosai and Ackerman's Surgical Pathology* (11th ed., Vols. 1–2). Elsevier

Paraneoplastic Pemphigus (PNP)

- Paraneoplastic autoimmune multiorgan syndrome (PAMS), first described as PNP – autoimmune vesicobullous, erosive mucocutaneous disease associated with an underlying malignancy
- Associated neoplasms:
  - Non-Hodgkin lymphoma – 42%
  - Chronic lymphocytic leukemia – 29%
  - **Castleman disease – 10%**
  - Thymoma – 6%
  - Spindle cell sarcoma – 6%
  - Waldenstrom macroglobulinemia – 6%
- Age of onset variable. Majority between ages of 45-70 yrs

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015

Paraneoplastic Pemphigus (PNP)

- Clinical features:
  - Intractable stomatitis– erosions & ulcerations in oropharynx extending to lips
  - Multiple organ systems involved
  - High rate of mortality from constrictive bronchiolitis obliterans
  - Diverse clinical presentations

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015

Paraneoplastic Pemphigus (PNP)

- Pathogenesis:
  - IgG autoantibodies against multiple antigens – plakin family, desmogleins and **Envoplakin**
  - Rare cases with clinical features of PNP in absence of detectable autoantibodies reported
  - Cytotoxic T cells play a prominent role in pathogenesis – high levels of CD8+ T cells in affected areas with increase in IL-6 (activates CD8+ T cells and CD56+ NK cells)

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015

Paraneoplastic Pemphigus (PNP)

- Histopathology:
  - Variable features – Combination of erythema multiforme-like, lichen planus-like, pemphigus vulgaris-like & pemphigoid-like features
  - **Suprabasal acantholysis** with basal apoptosis
  - Interface dermatitis
  - With or without bandlike infiltrate
  - May present exclusively with lichenoid interface dermatitis in absence of acantholysis
  - Subepidermal blister present in pemphigoid-like lesions

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015

Paraneoplastic Pemphigus (PNP)

- Direct immunofluorescence:
  - IgG in squamous intercellular substance with immune reactant deposition in DEJ
  - DEJ – Granular deposition of complement
  - Linear deposition of complement, IgG & IgM also identified
  - When present, basement membrane Ig & complement deposition distinguishes PNP from other forms of pemphigus (basement membrane deposits are generally not present)

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015

Paraneoplastic Pemphigus (PNP)

- Management:
  - Multidisciplinary care
  - Identification and management of underlying triggering malignancy
  - Monitoring and treatment of any lung disease
  - Active skin disease may respond to treatment of underlying malignancy. May require local or systemic immunomodulatory or suppressive therapy

Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI. Lever's histopathology of the skin. 11th ed. Philadelphia: Wolters Kluwer; 2015