NAVIGATING THE WHO-HAEM5 LYMPHOID LANDSCAPE:
AN IMAGING PRIMER FOR HEMATOLOGISTS

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WHO-HAEM5: What Changed, and Why It Matters

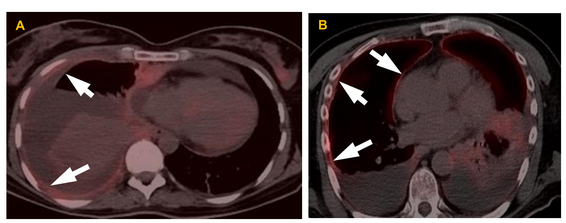
- **Integrated biology:** A shift beyond morphology-dominant classification toward incorporation of lineage, immunophenotype, molecular genetics and clinical context.
- **Diagnostic precision:** Organization across category → family/class → type → subtype, with refined diagnostic boundaries and terminology and the introduction, reassignment, consolidation or deletion of entities.
- **Biology-driven regrouping:** Unification of CNS, vitreoretinal and testicular LBCL as primary LBCL of immune-privileged sites, alongside expansion of the immune deficiency/dysregulation framework beyond PTLD.
- **Redefined boundaries:** Separation of transformed LBCL from de novo DLBCL, restriction of gray-zone lymphoma to mediastinal disease and removal of the age qualifier from EBV-positive DLBCL.
- **Expanded scope:** Inclusion of tumor-like B- and T-cell lesions, stroma-derived lymph node and splenic neoplasms, and germline predisposition syndromes.
- **Imaging relevance:** Whole-body distribution, sanctuary-site involvement and metabolic heterogeneity as indicators of concordance or discordance with the sampled entity and determinants of the most informative viable biopsy target.
- **Reporting implication:** Greater diagnostic specificity through inclusion of the WHO-HAEM5 entity and relevant immune, viral and molecular context, with reduced reliance on generic labels such as “lymphoma” or “lymphoproliferative disorder.”

What Radiology Offers

- **Whole-body Phenotype And Distribution**
  Spatial and temporal disease pattern across nodal, splenic, marrow/osseous, and extranodal sites, including involvement of immune-privileged sites that may alter management.
- **Biologic And Temporal Heterogeneity**
  Identifies discordance in avidity, growth, morphology, or treatment response that may raise concern for transformation, a second malignancy, infection, or treatment-related inflammation.
- **Imaging–Pathology Concordance**
  Discordance among imaging, pathology, and clinical behavior should prompt multidisciplinary review and consideration of additional tissue sampling.
- **Prognostication**
  Avidity, metabolic burden and response pattern on F-18 FDG PET-CT may predict behavior
- **Biopsy Selection**
  safest accessible, viable, and most informative lesion—preferably the one that is discordant in avidity, growth, morphology, or treatment response—while avoiding necrotic or previously treated tissue.
- **Urgent And Management-changing Findings**
  Detects organ, airway, vascular, spinal, bowel, or urinary compromise requiring urgent intervention.
- **Treatment Response And Residual Disease**
  Using Lugano criteria and the Deauville 5-point scale. Evaluates new uptake in the context of treatment timing, inflammation, treatment effect, and possible progression.

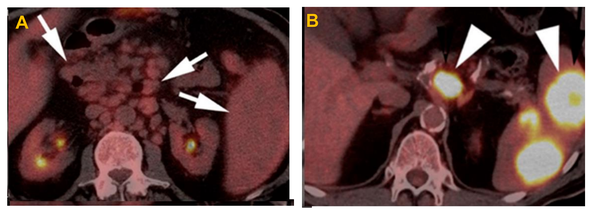
What Radiology Can Miss: Pitfalls and Limitations

- **Metabolic activity is not lymphoma-specific**: Infection, IgG4-related disease, sarcoid-like reactions and postprocedural or treatment-related inflammation may mimic lymphoma.
- **Avidity is treatment- and time-dependent:** Immune flare, G-CSF, marrow recovery, steroids and recent vaccination may substantially alter interpretation.
- **Transformation requires tissue:** Metabolic heterogeneity may identify the appropriate biopsy target but cannot replace histologic confirmation.
- **Residual mass or new uptake is not always active lymphoma**: Findings must be interpreted using distribution, treatment timing and response criteria.
- **Bone marrow assessment** is entity-dependent: PET can identify focal disease and guide biopsy but does not universally replace bone marrow sampling.
- **Discordance among imaging, pathology and clinical course** should prompt multidisciplinary review, interval reassessment or tissue confirmation.



Fluid Overload–Associated LBCL: Diffuse F-18 FDG uptake **confined to a pleural thickening/pleural effusion without a solid mass, or adenopathy**; fluid cytology confirmed FO-LBCL.

FO-LBCL is a newly recognized WHO-HAEM5 entity, defined by large B-cell lymphoma confined to a serous cavity effusion without an associated solid mass; the absence of solid disease is therefore a classification clue, not merely a negative imaging finding.
FO-LBCL typically occurs in **older, immunocompetent patients with chronic fluid-overload states** and usually shows an HHV8-negative, CD20-positive mature B-cell phenotype.
Fluid cytology/flow cytometry and HHV8 testing establish the diagnosis and distinguish FO-LBCL from primary effusion lymphoma.
^{18}F-FDG PET/CT confirms confinement to the serous cavity and excludes nodal or extranodal solid disease, helping establish the characteristic disease pattern and avoid misclassification as pleural metastasis or infection.

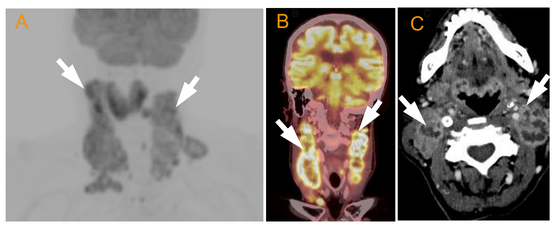


Large B-cell lymphomas arising from transformation of indolent B-cell lymphomas: Interval marked increase in nodal FDG avidity with new extranodal disease; biopsy confirmed transformation of indolent B-cell lymphoma to large B-cell lymphoma.
Progression of FL, MZL, or CLL/SLL to aggressive LBCL, including DLBCL or HGBL. **Transformation reflects additional genetic/epigenetic alterations and immune evasion**, frequently involving MYC, TP53, BCL2 and/or BCL6.

WHO-HAEM5 addresses **LBCL arising from transformation separately from de novo DLBCL**—typically more aggressive course .

Suspect with rapid nodal enlargement, new B symptoms, rising LDH, new extranodal disease, or disproportionate progression—often within 24 months of FL therapy.
Accelerated CLL can also show increased uptake and mimic transformation.

^{18}F-FDG PET/CT : abrupt increase in size and avidity; **SUVmax >10–15 may raise suspicion, but no universal threshold exists.** Biopsy remains the reference standard.



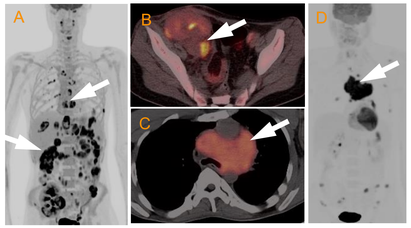
EBV-positive B-cell lymphoproliferative diseases (LPDs): Multiple intensely FDG-avid necrotic cervical lymph nodes with peripheral rim uptake; biopsy confirmed EBV-positive DLBCL.

EBV-positive DLBCL is recognized within the large B-cell lymphoma spectrum, with **EBV status forming an integral part of entity definition and clinical context.**

Typically presents with nodal and extranodal disease, often with B-symptoms; extranodal sites include the oropharynx, skin, lung, and gastrointestinal tract.

Prominent central necrosis with intense viable peripheral tumor may mimic infection or metastatic carcinoma; EBV-positive DLBCL generally demonstrates more aggressive features and more frequent extranodal involvement than DLBCL-NOS.

^{18}F-FDG PET/CT defines nodal and extranodal disease and directs biopsy toward the viable FDG-avid peripheral component rather than the necrotic center.



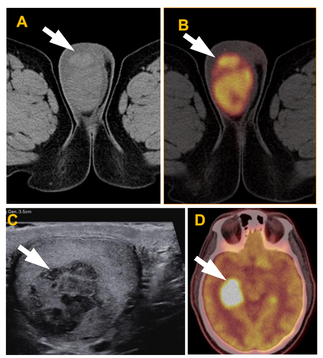
Post-Transplant Lymphoproliferative Disorder (PTLD): Multifocal FDG-avid **nodal and extranodal disease** after renal (A, B) and lung (C, D) transplantation, **arising near the transplant site.**

WHO-HAEM5 **groups PTLD with other immunodeficiency-related lymphoproliferations under “lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation**,” and recognizes polymorphic PTLD as a valid diagnostic category.

PTLD reflects iatrogenic immunosuppression; **risk is highest after small bowel or multiorgan transplant and lowest after bone marrow transplant.** Early disease (<1 year) is usually EBV-driven; late disease is more often EBV-negative and monomorphic.

Subtypes span nondestructive (may regress with reduced immunosuppression), polymorphic, monomorphic (DLBCL, BL, myeloma-like; most aggressive), and classical Hodgkin lymphoma–type.

^{18}F-FDG PET/CT maps nodal and extranodal extent and directs biopsy. Monomorphic PTLD shows the highest SUVmax among subtypes, but infection and inflammation mimic PTLD in immunosuppressed patients, so clinical correlation is essential



Primary Testicular Lymphoma: An intensely F-18 FDG-avid unilateral testicular mass; biopsy confirmed primary testicular lymphoma.

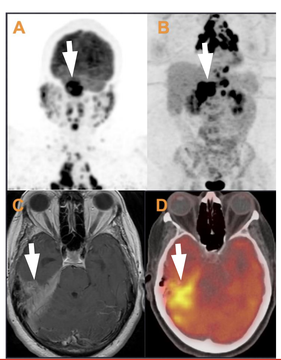
WHO-HAEM5 groups **testicular, CNS, and vitreoretinal large B-cell lymphomas as primary large B-cell lymphomas of immune-privileged sites, making anatomic site part of entity recognition**.

Arise in immune-privileged compartments shared biomolecular features, sharing **similar immune evasion characteristics**, i.e., loss of HLA expression and **tropism for the contralateral testis, CNS, and skin.**

Include primary CNS lymphoma (PCNSL), primary testicular lymphoma (PT-DLBCL), primary vitreoretinal lymphoma (PVRL)

Systemic staging is essential, and management typically incorporates CNS-directed and contralateral-testis–directed strategies

^{18}F-FDG PET/CT: helps exclude systemic disease and may reveal clinically occult extranodal involvement. In CNS disease, metabolic imaging may help distinguish viable lymphoma from treatment-related radiation necrosis.



IgG4-related disease: Multifocal F-18 FDG-avid involvement of the salivary and pituitary glands, dura, and retroperitoneum; biopsy confirmed IgG4-related disease.

WHO-HAEM5 places IgG4-related disease among **tumor-like lesions with B-cell predominance**, alongside reactive B-cell-rich lymphoid proliferations and Castleman disease, IgG4-related disease is a systemic immune-mediated fibroinflammatory disorder that spans metabolically active, mass-like inflammatory disease and less FDG-avid infiltrative fibrotic involvement.

Serum IgG4 elevation is not specific; diagnosis integrates characteristic organ involvement, elevated serum IgG4, and histopathologic lymphoplasmacytic infiltration.

^{18}F-FDG PET/CT maps whole-body disease extent, identifies the most metabolically active and representative biopsy site, and provides a baseline for treatment-response assessment

^{68}Ga-FAPI detects additional involved organs in about half of patients versus FDG. A combined 68Ga-FAPI-/18F-FDG PET index ≥1.5 predicts significantly shorter relapse-free survival.

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