

Epstein–Barr Virus

Infectious mononucleosis, immune response, and oncogenic associations

Morphology • pathogenesis • clinicopathologic interpretation

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Learning objectives

- Distinguish lytic EBV infection, latent B-cell infection, and the host cytotoxic response.
- Explain the blood, nodal, splenic, and hepatic changes in infectious mononucleosis.
- Construct a source-based diagnostic approach and recognize major complications.
- Connect deficient EBV immune control with selected EBV-associated malignancies.

EBV causes two very different clinical problems

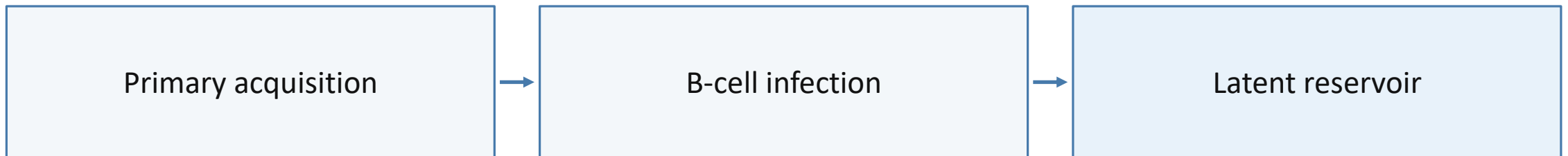
- Primary infection may cause self-limited infectious mononucleosis.
- Persistence in B lymphocytes establishes life-long latency.
- Impaired cellular surveillance permits pathologic B-cell expansion.
- EBV participates in the pathogenesis of selected lymphomas and carcinomas.

Acute reactive syndrome

Long-term persistence and tumors

EBV belongs to the herpesvirus family

- A human herpesvirus capable of latent infection following primary acquisition.
- Infected B lymphocytes constitute a major reservoir.
- The clinical phenotype reflects both viral gene expression and immune competence.



Age at first infection alters the presentation

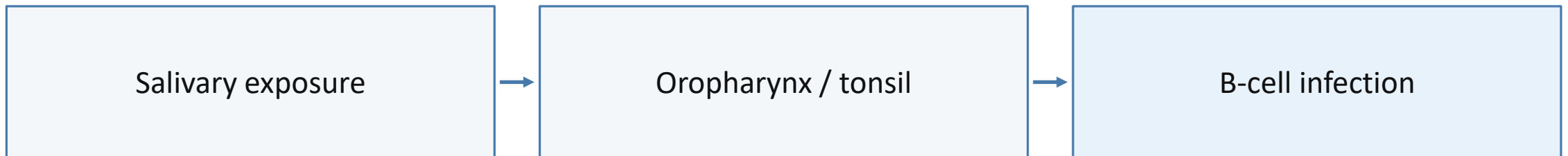
- Primary infection during childhood is often asymptomatic.
- Recognizable infectious mononucleosis is prominent in late adolescence and young adulthood.
- The clinical syndrome is related to development of the host immune response.

Childhood: Often silent

Later acquisition: Mononucleosis

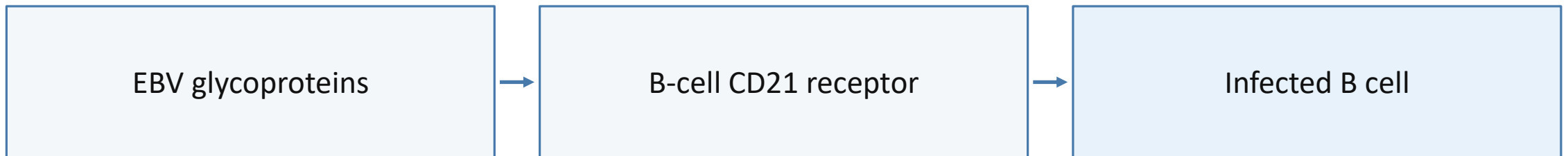
Saliva enables close-contact transmission

- EBV is frequently acquired by close human contact involving saliva.
- Tonsillar and oropharyngeal lymphoid tissue provides an early infection setting.
- This route links the clinical sore throat with lymphoid immune activation.



EBV enters B cells through CD21

- EBV surface glycoproteins bind the complement receptor CD21 on B cells.
- Receptor binding explains the strong B-cell tropism emphasized.
- The interaction initiates a program that may be lytic or latent.



Two infection programs: Lytic and latent

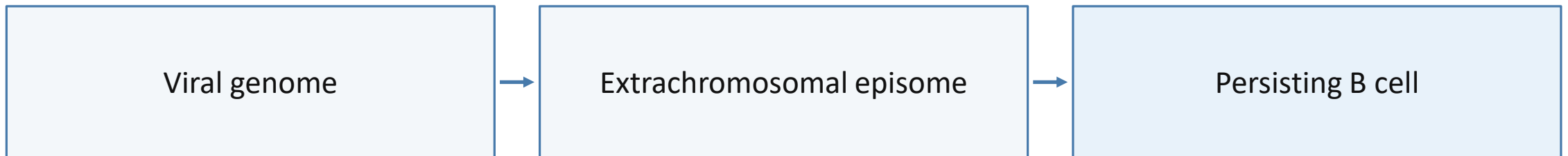
- In a minority of B cells, productive infection makes new virions and ends in lysis.
- In most infected B cells, EBV establishes latency rather than killing the cell.
- These alternatives produce different consequences for persistence and spread.

Lytic → progeny virions

Latent → persistent B cell

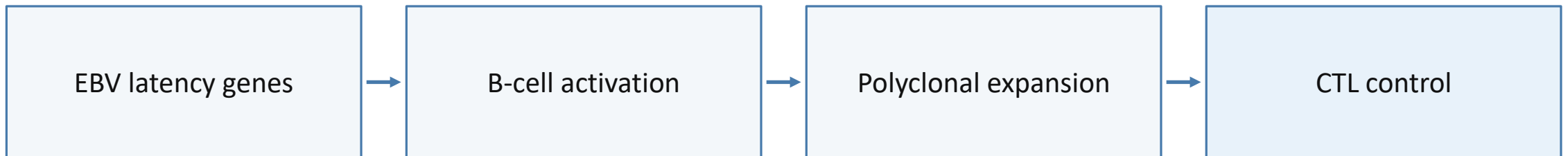
Latent EBV persists as an episome

- During latency, the viral genome remains extrachromosomal.
- The episome is compatible with host-cell survival and B-cell propagation.
- Latency is not synonymous with absence of viral gene expression.



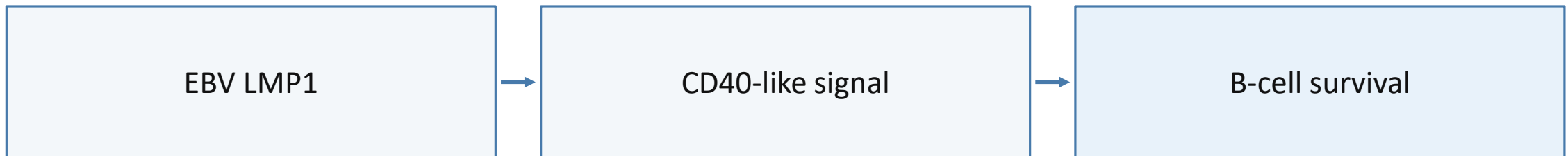
Latent proteins activate infected B cells

- LMP1 and EBNA2 promote B-cell activation, survival, and proliferation.
- This proliferation can initially be polyclonal rather than neoplastic.
- Effective cytotoxic immunity subsequently restrains activated infected cells.



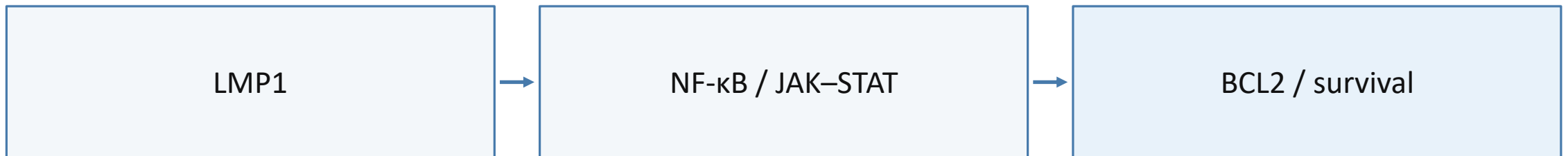
LMP1 imitates CD40 signaling

- LMP1 behaves as a constitutively active CD40-like signaling receptor.
- The cell receives growth-survival signaling without a conventional helper-T-cell stimulus.
- The resulting B-cell activation helps expand the infected compartment.



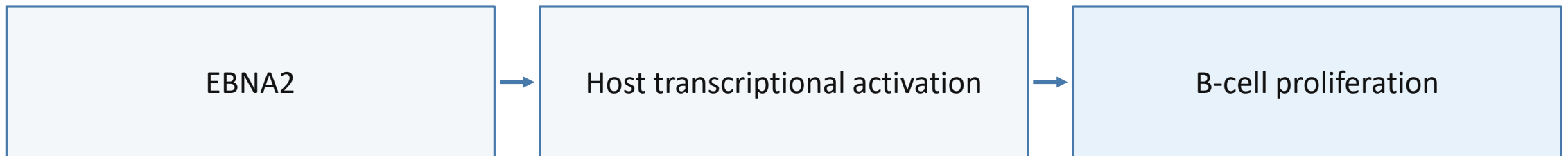
LMP1 engages pro-survival pathways

- LMP1 activates NF- κ B and JAK/STAT pathways.
- It also favors survival by upregulating anti-apoptotic BCL2.
- The combined effect is autonomous growth and reduced cell death.



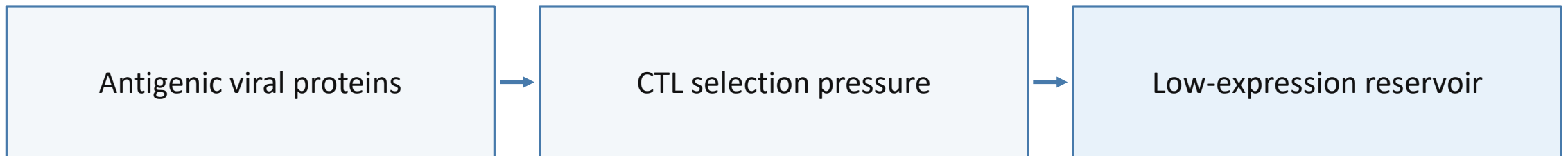
EBNA2 modifies host growth programs

- EBNA2 is a viral nuclear protein that mimics constitutive Notch-related signaling.
- Activation of host genes including cyclin D and SRC-family proto-oncogenes.
- EBNA2 complements LMP1 in immortalizing infected B cells.



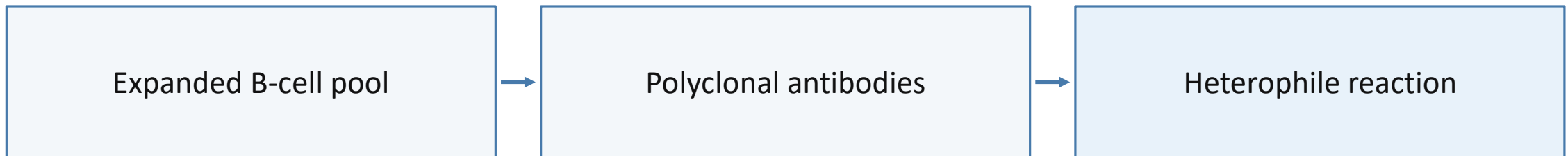
EBV must evade immune recognition to persist

- EBV encodes functions that reduce antigen presentation and impair effector responses.
- Cells strongly expressing immunogenic latency proteins are usually controlled.
- A minority that downregulates antigenic polypeptides can persist indefinitely.



Polyclonal B-cell activation generates antibodies

- Expanding infected B cells secrete antibodies of multiple specificities.
- Some bind sheep or horse erythrocytes: The heterophile antibodies.
- The resulting polyclonal response is central to the traditional Monospot test.



B-cell activation can produce autoantibodies

- Infected activated B cells may also produce antibodies against self-antigens.
- Antiplatelet antibodies can cause transient immune-mediated thrombocytopenia.
- This links an EBV infection mechanism to a hematologic complication.



Cytotoxic CD8 T cells dominate the response

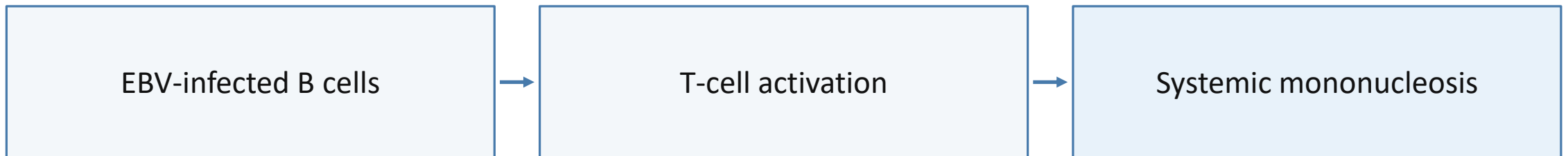
- Most circulating atypical lymphocytes are activated EBV-reactive CD8 T cells.
- NK cells also contribute to the reactive mononuclear population.
- These effector cells target infected B cells rather than representing EBV-infected tumor cells.

EBV-infected B cell

Reactive CD8 T cell

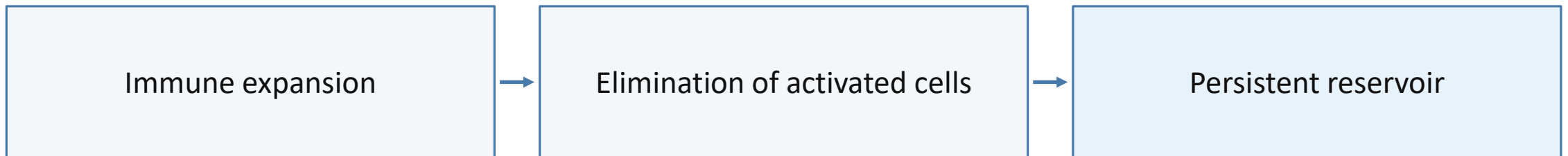
Immunopathology explains symptom onset

- Symptoms arise as the host cellular immune response intensifies.
- Reactive T-cell proliferation is centered in lymphoid tissues.
- The same response causes blood atypia, lymphadenopathy, and splenomegaly.



Most hosts control EBV but do not eradicate latency

- Humoral and cellular immunity curb viral shedding and B-cell expansion.
- B cells expressing many immunogenic latency proteins are eliminated.
- A small low-antigen-expressing B-cell reservoir survives long-term.



EBV-specific antibody classes evolve

- Early infection induces IgM responses against viral capsid antigens.
- IgG to viral antigens appears later and may persist throughout life.
- The timing and specificity of antibody responses inform diagnosis.

Early anti-VCA IgM



Later antiviral IgG



Long-term seropositivity

Natural history depends on immune balance

- Strong immune control may yield no overt illness or self-limited mononucleosis.
- Persisting latent cells normally remain under cellular surveillance.
- Loss of surveillance increases the possibility of EBV-driven B-cell proliferation.

Effective T-cell immunity

Impaired T-cell immunity

Age and exposure patterns are not uniform

- Early-childhood primary infection often causes little recognizable illness.
- Symptomatic mononucleosis is relatively prominent with later primary infection.
- Differences in age at acquisition across world settings.

Acquisition context	Typical presentation
Early-childhood infection	Frequently asymptomatic
Late adolescence / young adulthood	Classic infectious mononucleosis

Infectious mononucleosis: Clinical core

- Fever and sore throat accompany systemic lymphoid activation.
- Generalized lymphadenopathy is a characteristic finding.
- Splenomegaly and atypical lymphocytosis reinforce the diagnosis.

Fever / pharyngitis



Lymphadenopathy



Splenomegaly / atypia

Tonsillar inflammation reflects lymphoid activation

- Tonsillar and oropharyngeal lymphoid tissues show reactive changes.
- Local swelling is concordant with sore throat and pharyngitis.
- These changes are part of the systemic lymphoproliferative response.

Oropharyngeal symptoms

Reactive lymphoid expansion

Distribution of enlarged lymph nodes

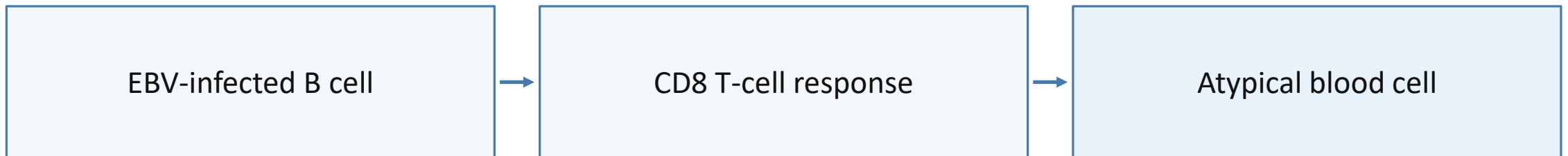
- Nodes are generally discrete and enlarged at multiple sites.
- Posterior cervical, axillary, and inguinal nodes are often involved.
- The broad distribution can clinically raise concern for lymphoma.

Posterior cervical

Axillary / inguinal

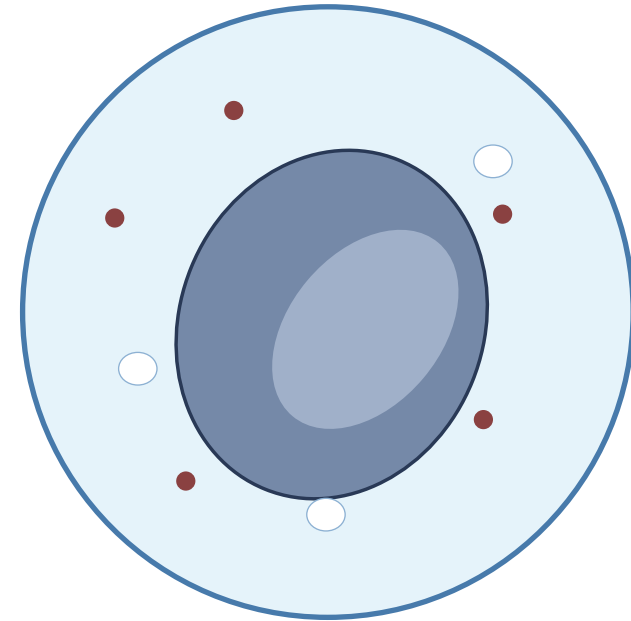
Atypical mononuclear cells are reactive

- The hallmark atypical blood cells are predominantly CD8-positive T lymphocytes.
- Their activation reflects an antiviral immune response.
- The viral reservoir is mainly in B cells: Cell-of-infection and cell-of-response differ.



Atypical lymphocyte: Microscopic appearance

- Abundant cytoplasm may contain clear vacuoles and azurophilic granules.
- Nuclei may be oval, indented, or folded.
- These features are suggestive in the appropriate clinical context, not exclusive to EBV.



Original cell schematic — not microscopy

Peripheral blood: Characteristic pattern

- An absolute lymphocytosis is typical of acute infectious mononucleosis.
- The supplied Robbins passage describes lymphocytes exceeding 60% of WBCs.
- Atypical forms may constitute a widely variable proportion of lymphocytes (5–80%).

Absolute lymphocytosis

Variable reactive atypia

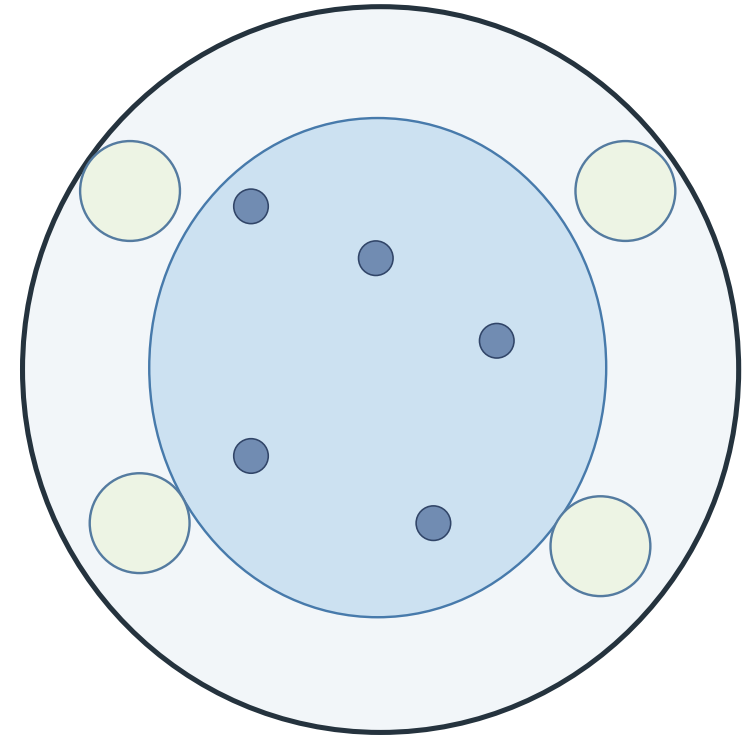
Do not confuse reactive atypia with malignancy

- Marked lymphocyte enlargement and nuclear irregularity can look alarming.
- Interpret peripheral blood with the full clinical syndrome and confirmatory testing.
- Reactive EBV lymphocytes are not, by themselves, proof of a lymphoid cancer.

Observation	Meaning in context
Large atypical lymphocytes	Common reactive antiviral response
Generalized adenopathy	May be benign or malignant
Clinical + EBV serology	Supports etiologic interpretation

Lymph nodes: Expansion of the paracortex

- Paracortical T-cell activation is the most striking nodal microscopic feature.
- Numerous immunoblasts may substantially distort the apparent architecture.
- B-cell follicles may show a lesser degree of reactive hyperplasia.



Expanded paracortex

Schematic; Not an H&E section

EBV-positive B cells are a minority in reactive nodes

- A minor paracortical population of infected B cells expresses latency-associated proteins.
- EBNA2 and LMP1 in these cells.
- Most activated large cells in this setting reflect the broader T-cell response.

Broad T-cell expansion

Minor EBV-positive B-cell pool

Reed–Sternberg-like cells are a pitfall

- Some EBV-infected reactive B cells resemble Reed–Sternberg cells.
- Morphologic resemblance alone does not establish Hodgkin lymphoma.
- Clinical course, architecture, and appropriate pathology workup remain essential.

RS-like reactive B cell

Hodgkin lymphoma: Not inferred

Florid EBV lymphadenitis may mimic lymphoma

- Reactive T-cell proliferation can be sufficiently exuberant to simulate malignancy.
- A single striking immunoblast or architectural abnormality is not definitive.
- The distinction requires integrated clinicopathologic interpretation.

Potential trap	Safer interpretation
Exuberant paracortical expansion	Can be reactive during EBV
RS-like B cells	Not sufficient for Hodgkin diagnosis
Short mononucleosis syndrome	Provides essential clinical context

Oropharyngeal lymphoid tissue parallels the nodes

- The tonsils can display the same active lymphoid proliferation as lymph nodes.
- This helps connect regional morphology with pharyngitis.
- The source describes the process as predominantly reactive rather than destructive.

T-cell activation



Tonsillar expansion



Sore throat

Splenomegaly is a major morphologic finding

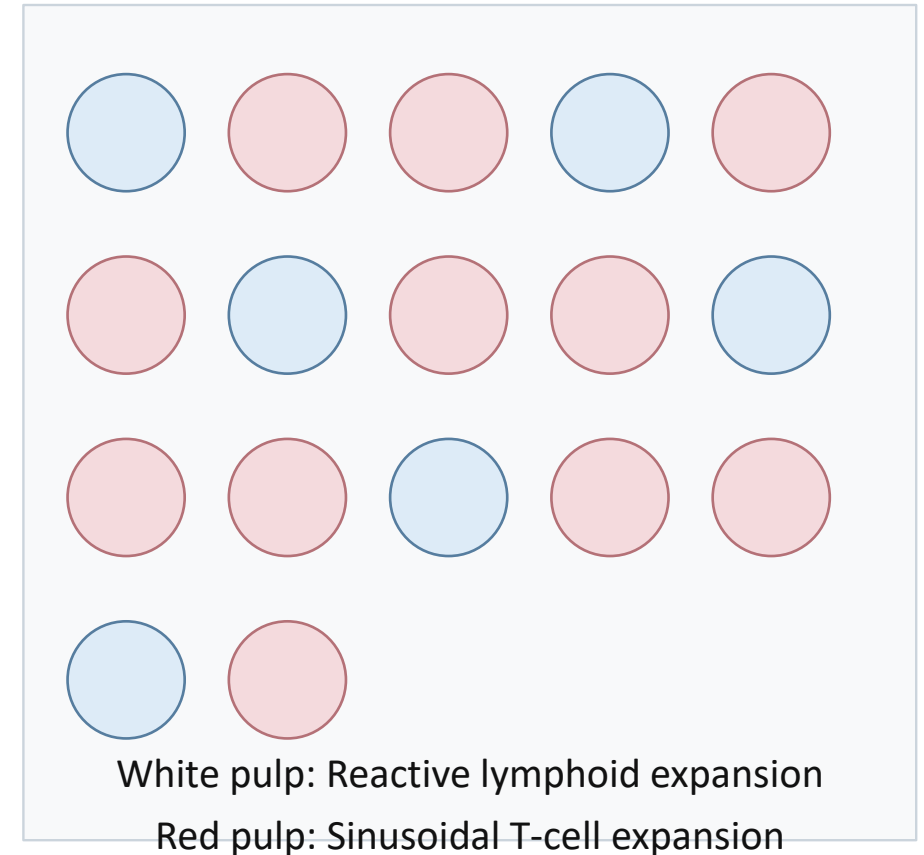
- The spleen is enlarged in most symptomatic cases.
- Typical spleen weights of approximately 300–500 g.
- The organ is often soft and fleshy with a hyperemic cut surface.

Enlarged, soft spleen

Hyperemic, fragile tissue

Splenic pulp contains activated lymphocytes

- White-pulp follicles and red-pulp sinusoids expand with activated T cells.
- These changes resemble the reactive processes seen in lymph nodes.
- Diffuse lymphoid activation accounts for increased spleen volume.



Why an enlarged spleen may rupture

- Rapid enlargement can stretch a tense, fragile splenic capsule.
- Rupture may occur after minor trauma and cause life-threatening hemorrhage.
- This uncommon complication is a clinically important consequence of the pathology.

Rapid enlargement



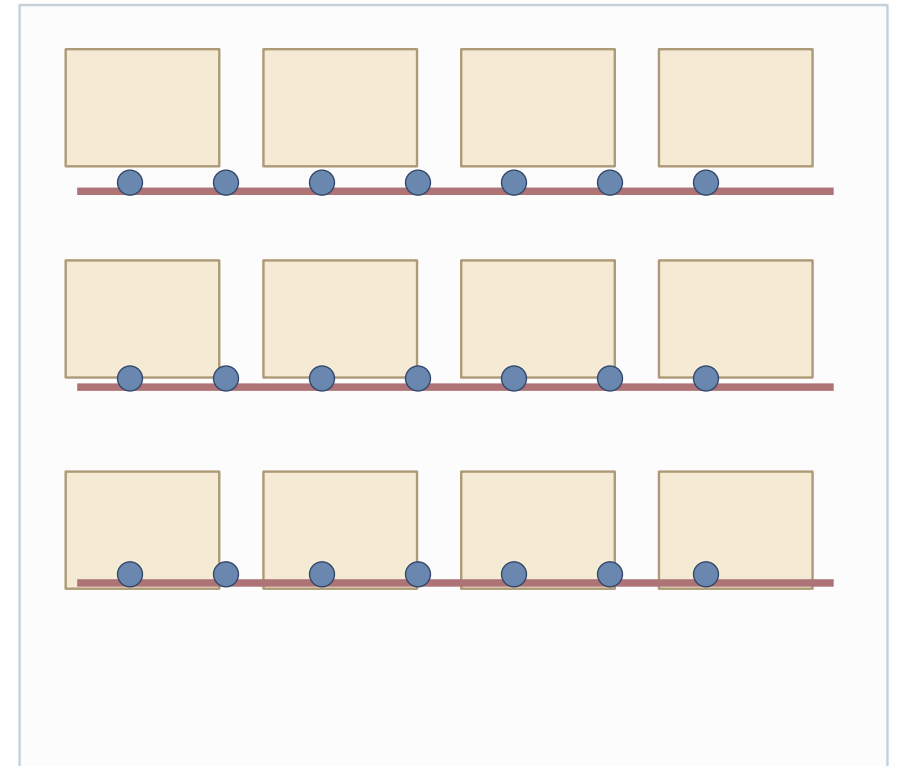
Capsular tension



Rupture / hemorrhage

The liver is frequently involved

- Hepatomegaly is generally moderate rather than massive.
- Atypical lymphocytes infiltrate portal areas and hepatic sinusoids.
- Occasional isolated or focal hepatocellular necrosis may accompany the infiltrate.



Hepatocyte cords and sinusoidal lymphocytes

EBV hepatitis may resemble other viral hepatitis

- Portal and sinusoidal mononuclear infiltration can produce a hepatitis pattern.
- Scattered parenchymal necrosis does not uniquely identify EBV.
- Clinical findings and EBV-specific evidence are needed to resolve the cause.

Lymphocytic inflammation

Focal hepatocellular injury

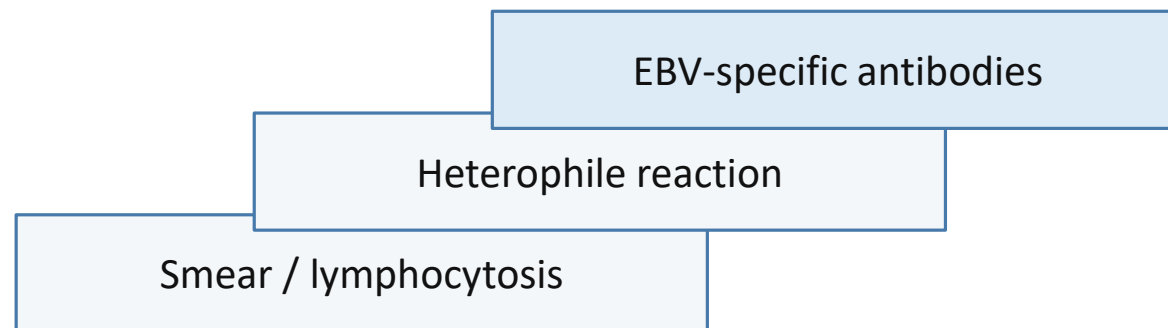
EBV can affect organs beyond lymphoid tissue

- Occasional involvement of the CNS, lungs, and other organs.
- Meningoencephalitis and pneumonitis are among possible manifestations.
- These are less typical than lymphoid, hematologic, and hepatic changes.

Site	Manifestation in Robbins
Blood / lymphoid organs	Atypia, adenopathy, splenomegaly
Liver	Hepatitis / occasional jaundice
CNS or lung	Less common inflammation

The diagnostic evidence forms a hierarchy

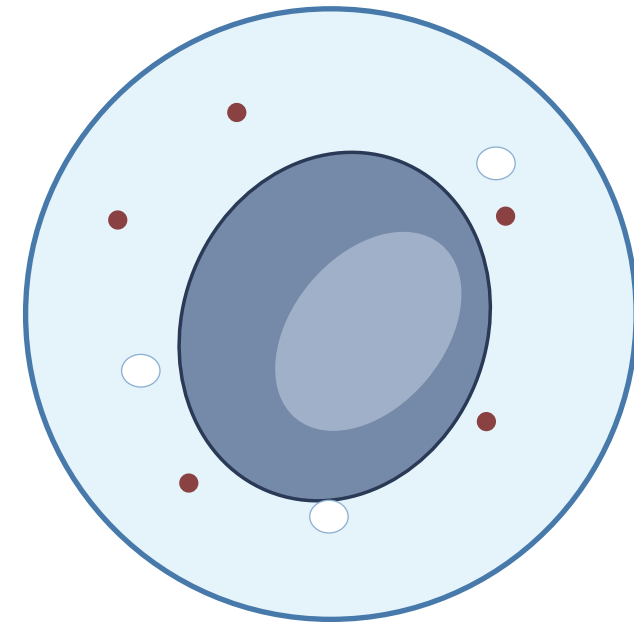
- First, recognize characteristic atypical lymphocytosis in the clinical setting.
- Next, a heterophile antibody test provides supporting evidence.
- EBV antigen-specific antibodies provide more specific etiologic information.



Increasing etiologic specificity →

Peripheral smear is an early clue, not final proof

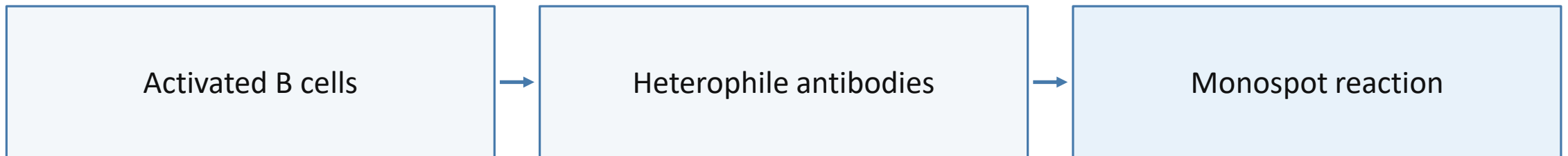
- Large reactive lymphocytes strongly suggest a mononucleosis syndrome.
- This blood pattern arises from immune activation, not directly from virion production.
- Combine morphology with clinical and serologic evidence.



Original cell schematic — not microscopy

The heterophile test detects a polyclonal effect

- EBV-activated B cells can produce antibodies reactive with animal erythrocytes.
- The Monospot reaction interrogates these heterophile antibodies.
- The reaction after blood morphology and before antigen-specific serology in specificity.



EBV-specific serology adds etiologic specificity

- The supplied source identifies viral capsid, early, and nuclear antigens as targets.
- Early anti-capsid IgM and later IgG reflect evolution of the host response.
- Interpret results in relation to clinical timing, not as isolated labels.

Antigen / response	Textbook relevance
Viral capsid antigen (VCA)	Early IgM; later IgG
Early antigen	Part of EBV-specific diagnostic testing
Epstein–Barr nuclear antigen	Part of EBV-specific diagnostic testing

Synthesize the diagnostic findings

- Clinical context: Fever, sore throat, lymphadenopathy, and splenomegaly.
- Blood: Absolute lymphocytosis with reactive atypical lymphocytes.
- Laboratory: Heterophile reaction and, where needed, EBV-specific antibody pattern.

Compatible syndrome



Reactive hematology



Etiologic antibody support

CMV may produce a similar mononucleosis syndrome

- CMV can cause fever, atypical lymphocytosis, adenopathy, and hepatitis.
- Symptom overlap means atypical lymphocytes alone cannot establish EBV.
- The neighboring Robbins CMV section emphasizes serologic diagnosis.

Clinical feature	EBV mononucleosis	CMV mononucleosis
Fever / fatigue	Present	Present
Atypical lymphocytes	Present	Present
EBV-specific serology	Diagnostic evidence	Does not establish CMV

Lymphoma and leukemia enter the differential

- Fatigue, lymphadenopathy, and atypical circulating cells can prompt concern for malignancy.
- EBV nodal immunoblasts may produce an alarming lymphoma-like appearance.
- Avoid relying on one morphologic feature without clinical and diagnostic correlation.

Reactive EBV proliferation

Neoplastic proliferation

Hepatitis and exanthems complicate recognition

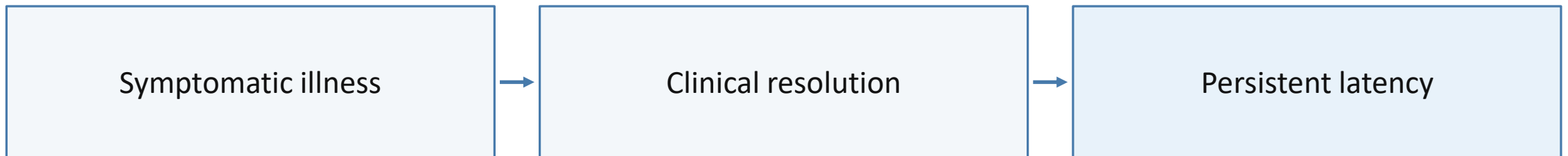
- Hepatic involvement may mimic hepatotropic viral disease.
- A febrile rash can resemble other childhood viral exanthems.
- The combination of lymphoid findings and EBV-specific laboratory support is useful.

Hepatitis-like syndrome

Febrile viral exanthem

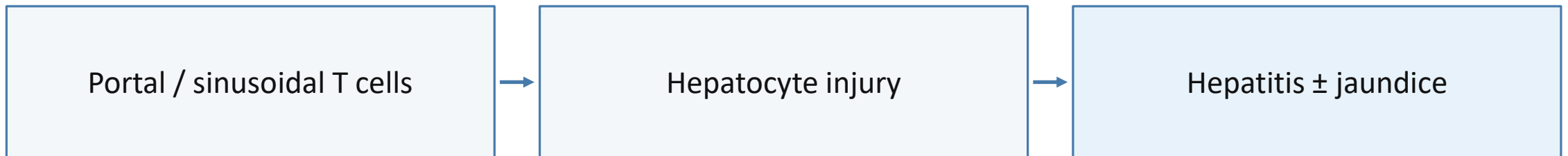
The expected course is usually self-limited

- Most patients recover from mononucleosis within approximately 4–6 weeks.
- Fatigue may continue after other signs have subsided.
- The illness resolves even though latent EBV infection persists.



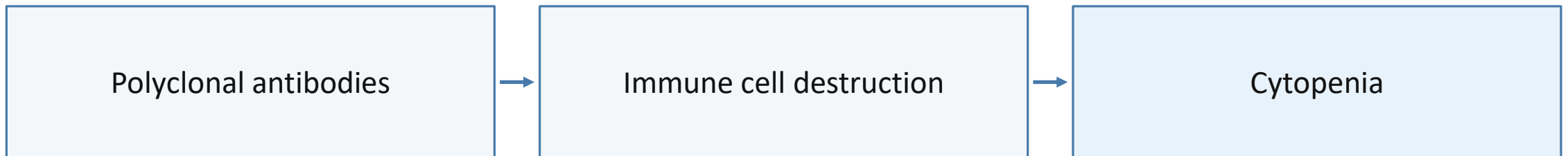
Hepatic manifestations range in severity

- Hepatosplenomegaly and biochemical or clinical hepatitis commonly occur.
- Jaundice can accompany hepatic involvement.
- In the supplied source, necrosis is generally scattered or focal.



Immune cytopenias are less common complications

- Immune cytopenias among the less frequent consequences.
- Polyclonal B-cell activation offers a mechanism for antiplatelet autoantibodies.
- This differs mechanistically from cytopenia caused by direct marrow replacement.



EBV can trigger hemophagocytic lymphohistiocytosis

- HLH is listed as a rare, serious complication of EBV infection.
- The key concept is pathologic immune activation rather than routine viral cytopathy.
- Suspected HLH requires separate diagnostic evaluation beyond a basic EBV test.

Routine reactive response

Severe dysregulated inflammation

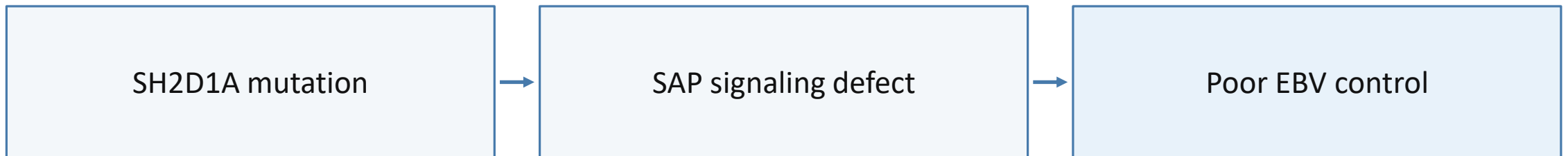
Extra-lymphoid complications broaden the differential

- Abnormalities affecting the nervous system and lungs.
- Kidney, marrow, eye, and cardiac complications are also described.
- These manifestations are unusual and should not be mistaken for the typical course.

Complication spectrum	Clinical meaning
Meningoencephalitis	Neurologic involvement
Pneumonitis	Pulmonary involvement
Other organ dysfunction	Broader but less frequent disease

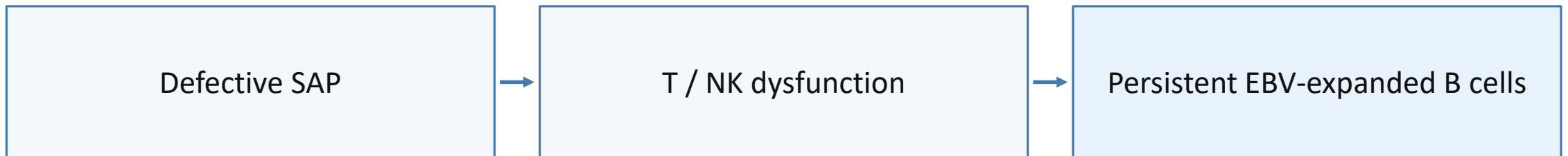
X-linked lymphoproliferative disease: Inherited susceptibility

- Defects in SH2D1A can cause ineffective control of EBV infection.
- SH2D1A encodes SLAM-associated protein (SAP), an immune signaling adaptor.
- The phenotype may become apparent only after a significant EBV infection.



SAP dysfunction impairs cellular immunity

- SAP participates in activation pathways of T cells, NK cells, and B cells.
- Reduced cytotoxic immune activation undermines elimination of infected B cells.
- The related Robbins immunodeficiency chapter also links SAP to Tfh-cell function.



Severe outcomes in X-linked lymphoproliferative disease

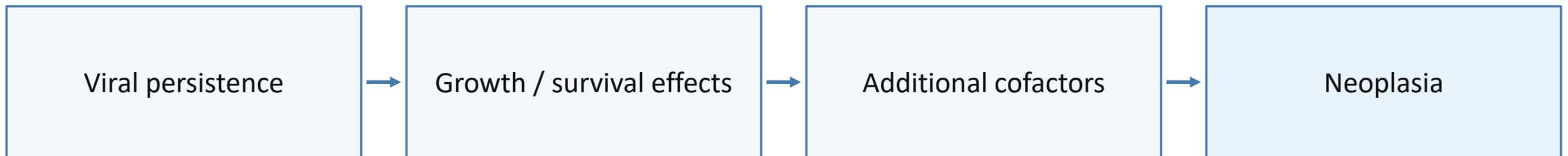
- Acute EBV infection may become overwhelming and potentially fatal.
- Some patients develop EBV-positive B-cell lymphoma.
- Hypogammaglobulinemia can predispose to other infections.

Fulminant EBV disease

Lymphoma / antibody deficiency

EBV oncogenesis is context-dependent

- EBV-associated cancers include selected B-cell lymphomas and carcinomas.
- Viral latency proteins may drive cell survival and proliferation.
- Additional genetic, environmental, or immunologic factors often matter.



Malignant transformation is not inevitable

- Most people infected with EBV do not develop an EBV-associated tumor.
- Cytotoxic T-cell surveillance usually controls antigenic EBV-driven expansion.
- Cancer development reflects interaction of immune context and other transforming events.

Common: Controlled latency

Rare: Malignant outgrowth

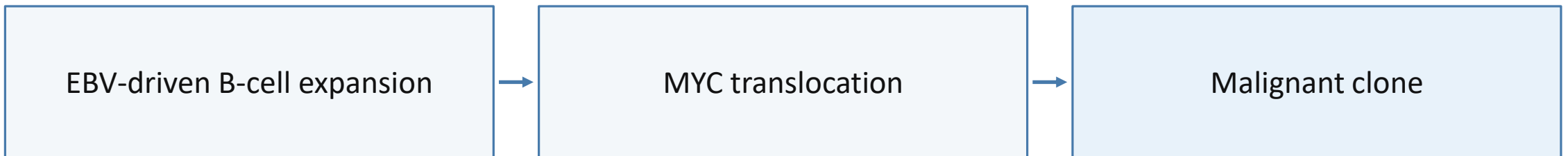
Endemic Burkitt lymphoma has a strong EBV association

- Latent EBV in more than 90% of endemic Burkitt lymphomas.
- EBV is less common in morphologically similar nonendemic tumors.
- Geographic and environmental cofactors affect the strength of the association.

Burkitt context	EBV detected in tumors
Endemic regions	>90% (Robbins)
Outside endemic regions	15–20% (Robbins)

Burkitt oncogenesis requires cooperating events

- EBV can sustain an expanded B-cell pool in which mutations can accumulate.
- Dysregulation of MYC, usually by chromosomal translocation, is central.
- The text emphasizes EBV as a facilitator rather than a sole direct cause of Burkitt lymphoma.



Burkitt tumors restrict antigenic EBV proteins

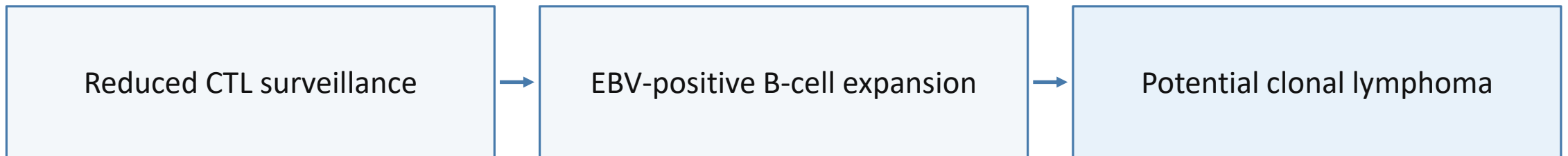
- Burkitt lymphoma cells generally lack the LMP1 and EBNA2 pattern of fully transformed B cells.
- This contrasts with the antigenically broad latency program in early infected B cells.
- Restricted viral antigen expression helps explain persistence despite immune pressure.

Early activated B cell: LMP1 / EBNA2

Burkitt cell: Restricted latency

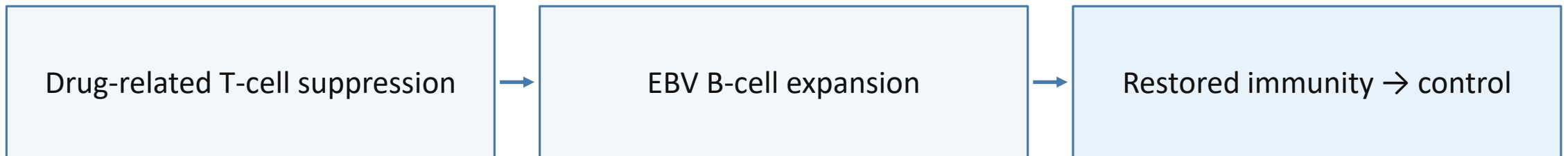
Immunosuppression favors EBV-positive B-cell tumors

- Defective T-cell surveillance permits proliferation of EBV-infected B cells.
- Such proliferations may begin polyclonally and progress to monoclonal neoplasia.
- , these tumors often express LMP1 and EBNA2 and typically lack MYC translocations.



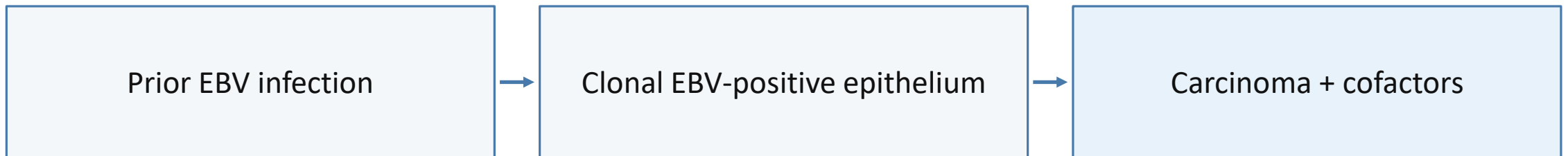
Restoring T-cell surveillance may constrain proliferation

- Some EBV-related B-cell proliferations arise during post-transplant immunosuppression.
- Reduction of immunosuppressive drugs can permit control in some cases.
- The essential concept is immune dependence; No treatment algorithm is inferred here.



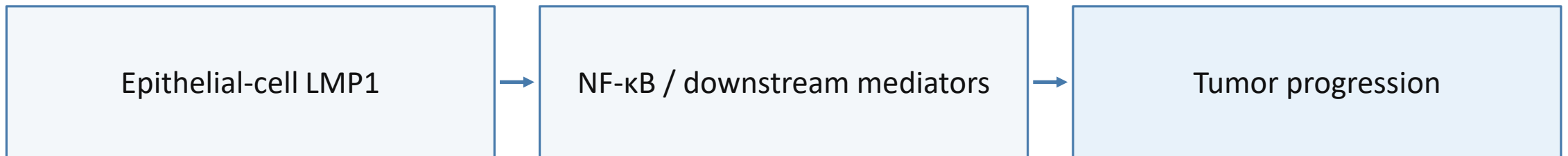
Nasopharyngeal carcinoma has a strong EBV link

- EBV genomes in nasopharyngeal carcinomas worldwide.
- Clonal viral genomes within tumors support infection before clonal tumor expansion.
- Geographic concentration points to contributions from additional cofactors.



LMP1 affects epithelial tumor biology

- LMP1 can activate NF- κ B signaling in EBV-associated nasopharyngeal carcinoma.
- Increased VEGF, FGF2, MMP9, and COX2 among potential downstream mediators.
- Tumor immune-evasion pathways can limit an otherwise conspicuous T-cell infiltrate.



Other tumor associations remain important

- EBV-associated Hodgkin lymphoma elsewhere in the text.
- EBV-positive carcinomas may also occur in sites such as stomach or thymus.
- Association does not mean that every example of a named tumor is EBV-driven.

Tumor category	Textbook association
Selected B-cell lymphomas	Variable EBV prevalence and latency
Nasopharyngeal carcinoma	Strong EBV association
Some other carcinomas / Hodgkin lymphoma	EBV-associated subsets

Case 1: Acute infectious mononucleosis

- A young adult has fever, sore throat, fatigue, and posterior cervical adenopathy.
- Blood testing shows absolute lymphocytosis with large reactive cells.
- Question: Which cell population explains the atypical circulating lymphocytes?

Case 1: The atypical cells are activated T cells

- Most conspicuous circulating atypical lymphocytes are CD8-positive reactive T cells.
- They expand in response to EBV-infected B cells.
- The diagnostic argument strengthens with heterophile and EBV-specific serology.



Case 2: Alarming lymph-node biopsy

- An EBV-compatible febrile illness is accompanied by a rapidly enlarged node.
- The biopsy shows paracortical immunoblasts and occasional RS-like cells.
- Question: What error should be avoided before a lymphoma diagnosis is made?

Case 2: Integrate morphology and clinical setting

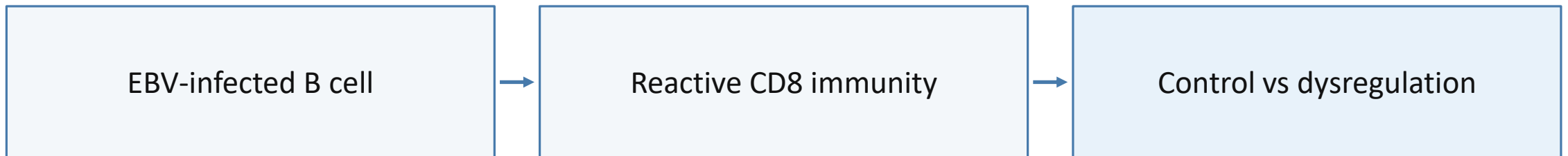
- Acute EBV lymphadenitis can closely resemble a lymphoma.
- RS-like cells and a florid paracortex are not sufficient for malignancy.
- Interpret architecture, clinical course, and confirmatory workup together.

Reactive EBV lymphadenitis

Malignancy: Requires independent proof

One mechanism explains diverse manifestations

- Infected B cells and their latent gene products initiate proliferation.
- Activated CD8 T cells account for the characteristic blood and lymphoid morphology.
- Immune control usually yields recovery; Immune failure increases severe infection and tumor risk.



Selected textbook references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Infectious Diseases: Epstein–Barr virus, infectious mononucleosis, and tissue morphology.
- Neoplasia: EBV-associated lymphomas and nasopharyngeal carcinoma.
- Immune disorders: X-linked lymphoproliferative disease.