

Chronic inflammation and lymphoid neoplasia

How persistent immune stimulation can create a setting for lymphoma

Pathologic mechanisms • clinicopathologic correlations

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Learning objectives

- Explain why persistent local immune stimulation can predispose to lymphoid neoplasia.
- Connect gastric MALT lymphoma, celiac-associated T-cell lymphoma, and implant-associated lymphoma to their inflammatory settings.
- Distinguish antigen-dependent growth from genetically autonomous lymphoma.
- Contrast localized inflammation with HIV-associated systemic immune dysregulation.

This topic is about lymphomagenesis—not generic inflammation

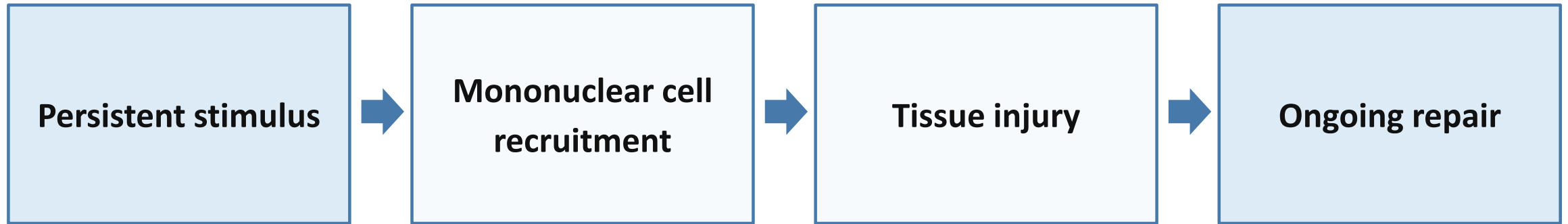
Central question

- Which chronic immune states predispose to lymphoma?
- Why do some tumors arise at the inflamed site?
- How can a reactive lymphoid expansion become neoplastic?

Scope boundary

- Mechanisms and specific clinicopathologic examples
- Contrasts with HIV-linked systemic lymphoma risk
- General chronic inflammation is used only as background

Chronic inflammation: Injury and repair coexist



Unlike transient acute inflammation, the stimulus and response persist or recur over time.

The histologic setting of a persistent immune response

Inflammatory infiltrate

Macrophages,
lymphocytes and plasma
cells.

Tissue injury

Persistent agent and
immune mediators
damage tissue.

Repair response

Angiogenesis and fibrosis
may accompany the
infiltrate.

Persistent triggers are biologically diverse

Infection

Difficult-to-eradicate
microbes sustain
responses.

Immune dysregulation

Autoimmune and
hypersensitivity reactions
recur.

Persistent material

Nondigestible or other
enduring stimuli may
maintain injury.

Localized inflammation and systemic dysregulation differ

Feature	Localized inflammatory setting	Systemic HIV-associated setting
Distribution	Prolonged stimulus within a tissue	T-cell dysregulation or immunodeficiency
Typical tumor relationship	Lymphoma often originates at inflamed site	B-cell lymphoma can arise in many organs
Illustrative contexts	Stomach, intestine, implant-associated site	HIV infection / AIDS

Four settings to lymphoma risk

H. Pylori

Gastric B-cell lymphoma

Gluten-sensitive enteropathy

Intestinal T-cell lymphoma

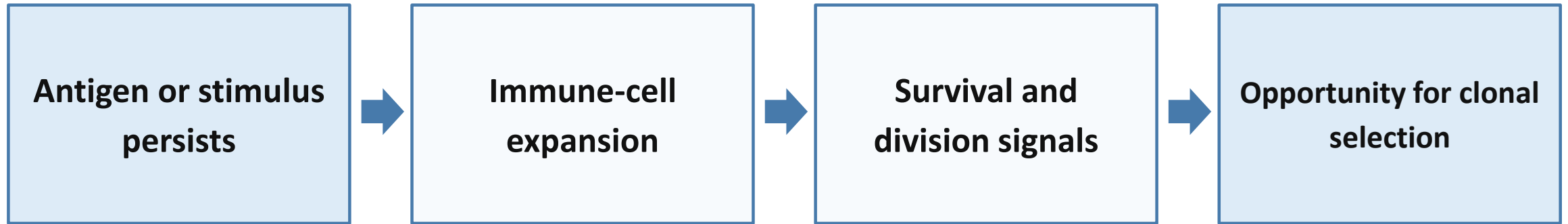
Breast implants

Unusual T-cell lymphoma

HIV infection

B-cell lymphomas at varied sites

From chronic stimulus to a permissive tissue niche



A predisposing environment is not equivalent to a malignant clone.

Repeated proliferation increases opportunities for mutation

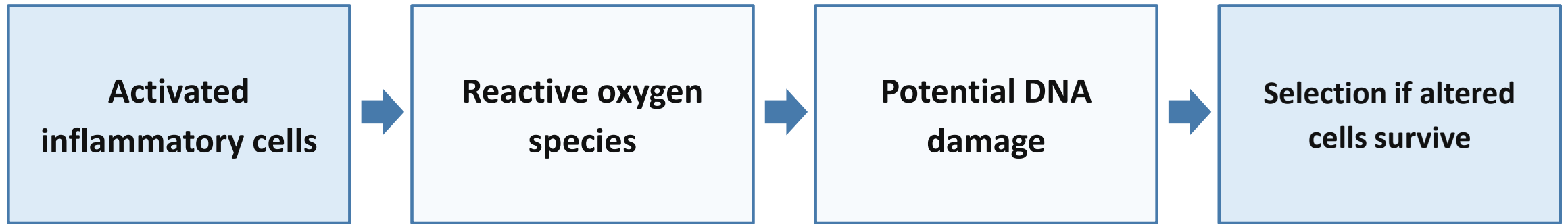
Biologic rationale

- Immune activation repeatedly recruits cells into proliferation.
- Replicating cells may acquire somatic genetic changes.
- More rounds of division increase opportunities for selection.

Important distinction

- Chronic inflammation raises risk; It does not automatically cause cancer.
- Acquired transforming events are still needed.
- Risk mechanisms vary with cell lineage and site.

Inflammatory cells can create genomic stress



This is a general inflammation–cancer mechanism, not a demonstrated unique cause of every listed lymphoma.

Survival signaling changes the consequences of DNA damage

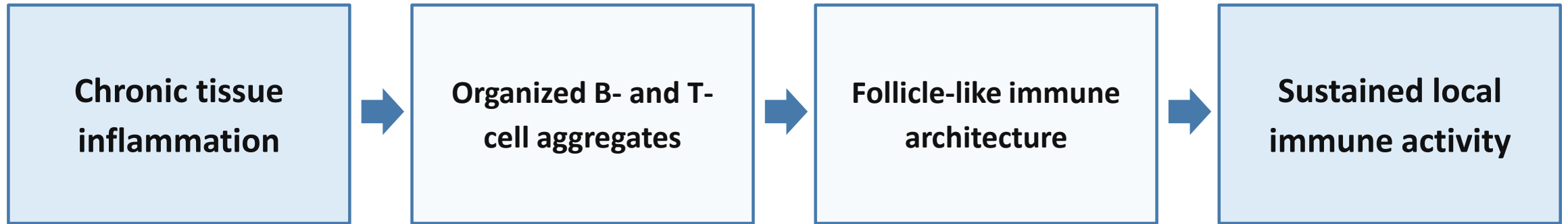
Inflammatory mediators

- Promote continued immune-cell recruitment.
- Support activated-cell survival.
- May allow damaged cells to persist.

Cancer-enabling context

- Clonal expansion requires growth or survival advantages.
- Genomic lesions can cooperate with the inflammatory milieu.
- These are convergent, not interchangeable, processes.

Tertiary lymphoid structures form outside lymphoid organs



H. Pylori gastritis can create mucosal collections resembling lymphoid tissue normally seen elsewhere.

Normal germinal-center reactions involve DNA modification

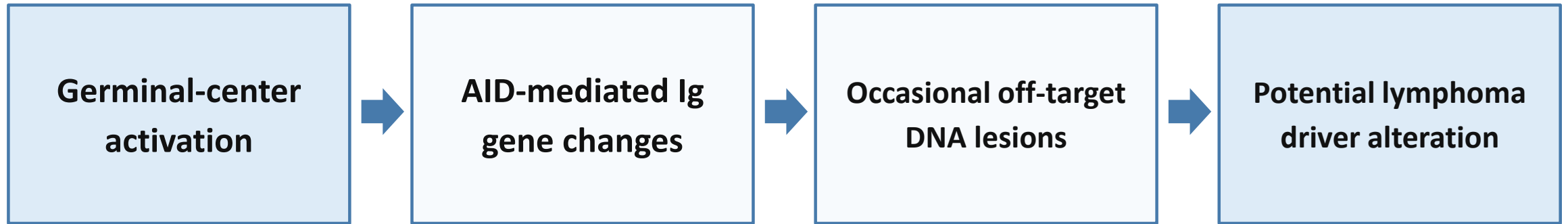
Physiologic adaptation

- Antigen activation drives germinal-center B-cell proliferation.
- Activation-induced cytidine deaminase (AID) acts on immunoglobulin genes.
- Class switching and somatic hypermutation diversify antibodies.

Pathologic opportunity

- DNA breakage and off-target lesions may occur.
- Proto-oncogene translocations and point mutations can arise.
- The same diversification machinery may increase oncogenic risk.

AID links normal immune diversification to oncogenic lesions

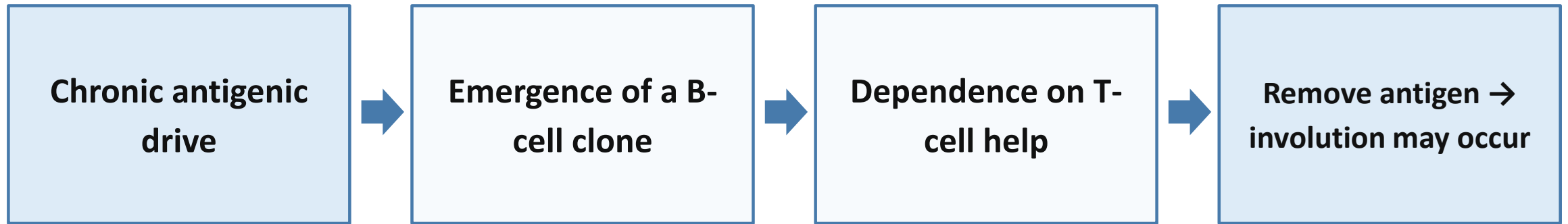


MYC::IGH rearrangements and BCL6 alterations as illustrative consequences.

Clonal evolution is distinct from reactive hyperplasia

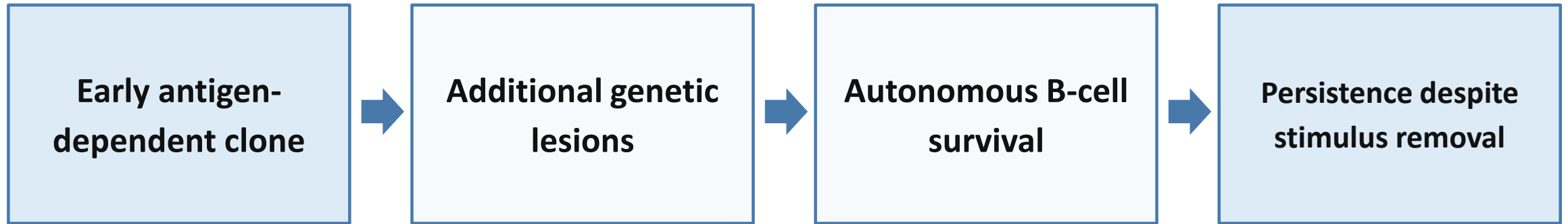
Property	Reactive immune proliferation	Neoplastic lymphoid clone
Cell population	Typically polyclonal	Clonal expansion after genetic change
Growth input	Depends on normal immune signals	May be antigen-dependent initially
Evolution	Can regress with resolution	May become autonomous with further lesions

An antigen-dependent lymphoma may still regress



This is a characteristic early model of extranodal marginal zone lymphoma, not a universal response pattern.

Later mutations can remove dependence on the stimulus



BCL10/MALT1 pathway dysregulation is one route described for extranodal marginal zone lymphoma.

Inflammation is a risk setting, not a diagnosis

Association

Recognize the tissue-specific clinical link.

Causation

Identify plausible pathways without claiming inevitability.

Diagnosis

Demonstrate a genuine neoplasm; Inflammation alone is insufficient.

Anatomic context predicts which lymphoma to suspect

Inflammatory site	Persistent stimulus	Associated lymphoid neoplasm
Stomach	Helicobacter gastritis	Extranodal marginal zone B-cell lymphoma
Small intestine	Gluten-sensitive enteropathy	Enteropathy-associated T-cell lymphoma
Breast implant setting	Implant-associated chronic inflammation (possible link)	Implant-associated anaplastic large cell lymphoma

H. Pylori gastritis: The prototype of local lymphomagenesis

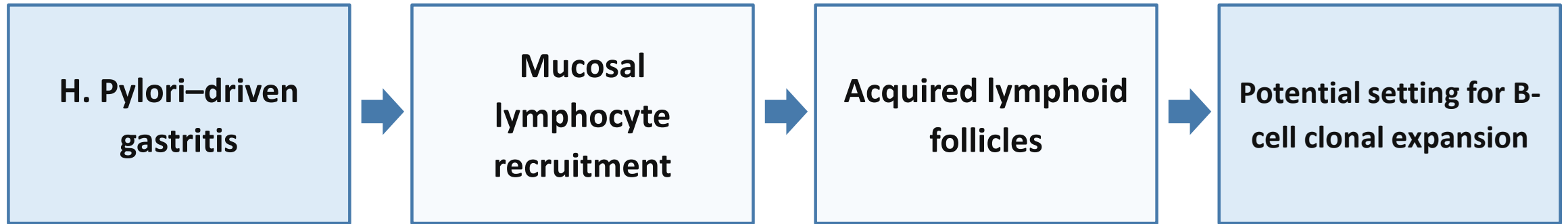
Underlying setting

- Chronic gastric infection provides sustained antigenic stimulation.
- The normal stomach lacks organized MALT.
- Inflammation can induce mucosal lymphoid aggregates.

Lymphoma relationship

- Gastric extranodal marginal zone B-cell lymphoma is strongly linked to this setting.
- Most gastric MALT lymphomas occur with H. Pylori infection.
- Localized disease can retain dependence on the stimulus.

The inflamed stomach acquires organized lymphoid tissue



The appearance of acquired MALT does not by itself establish lymphoma.

Gastric MALT lymphoma arises from a B-cell compartment

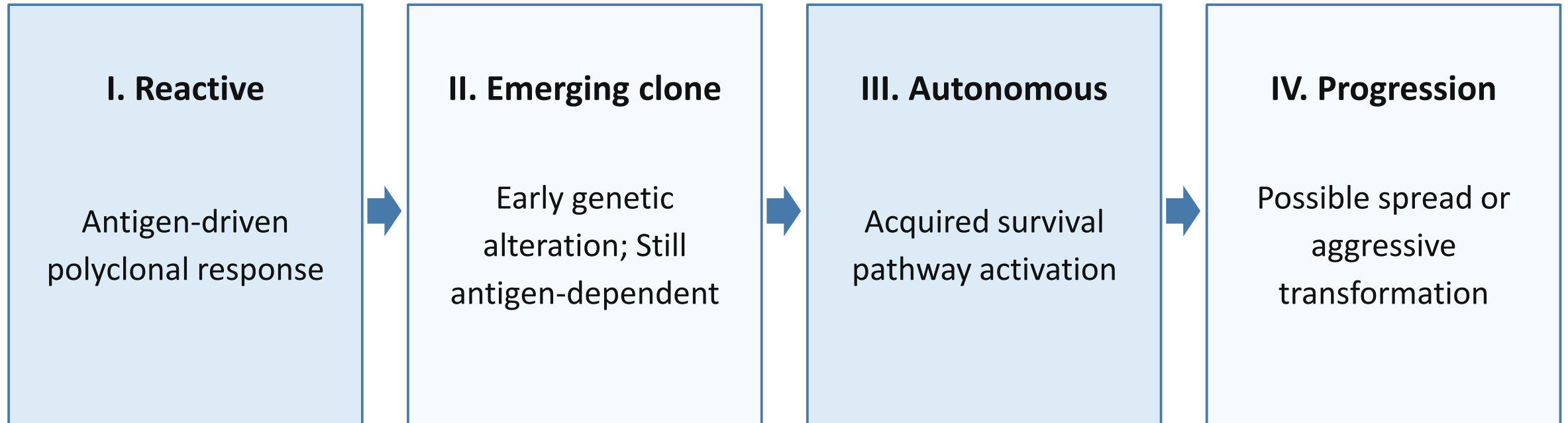
Cell lineage

- Extranodal marginal zone lymphoma is a mature B-cell tumor.
- Most show somatic hypermutation.
- A memory B-cell origin is considered likely.

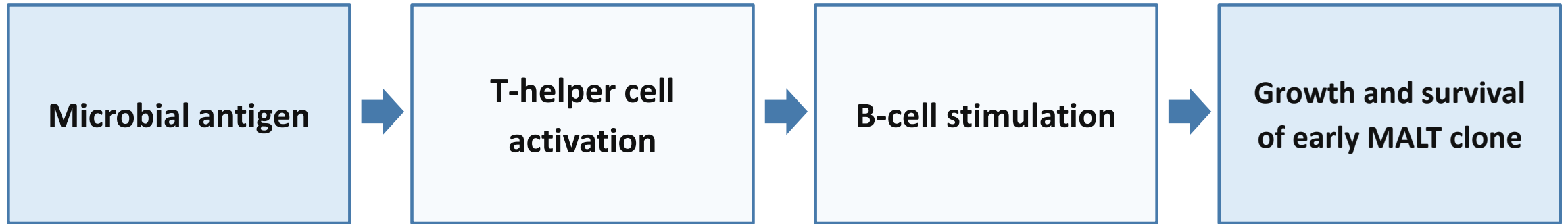
Anatomic behavior

- Often arises in tissues involved by chronic inflammation.
- May remain localized for extended periods.
- Systemic dissemination may occur later.

Polyclonal-to-monoclonal evolution: An instructive model



The MALT microenvironment can sustain a lymphoma clone



The first neoplastic clone need not be immediately antigen-independent.

Gastric MALT lymphoma: Characteristic tissue pattern

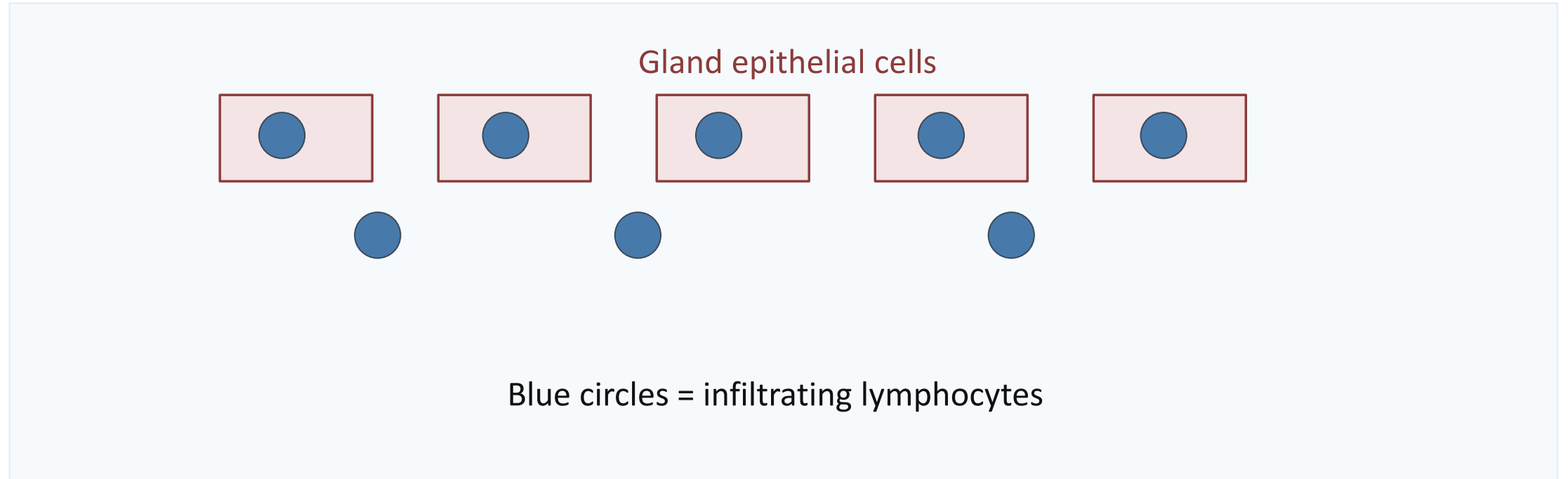
Microscopic observations

- Dense lymphocytic infiltration of lamina propria.
- Neoplastic cells infiltrate gastric glands.
- The resulting gland involvement forms lymphoepithelial lesions.

Additional features

- Reactive-appearing B-cell follicles may persist.
- Plasmacytic differentiation can occur.
- These features must be interpreted in the biopsy context.

Lymphoepithelial lesions reflect gland infiltration



Simplified schematic—not a histologic image: Neoplastic lymphocytes infiltrate gastric gland epithelium.

B-cell markers support the lineage of gastric MALT lymphoma

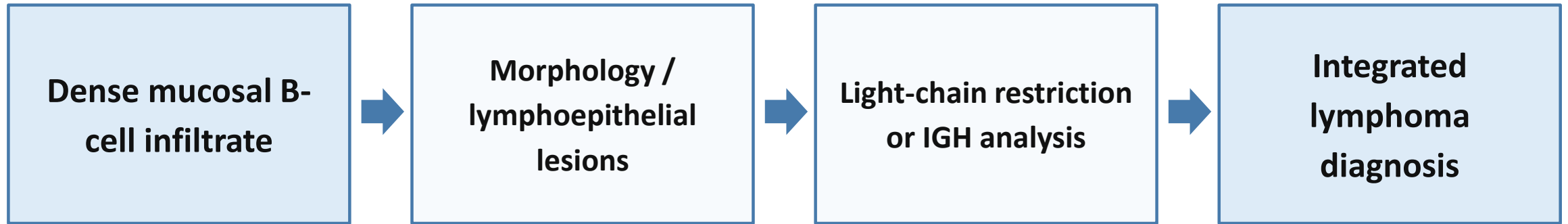
Characteristic pattern

- Expression of B-cell markers CD19 and CD20.
- Typically negative for CD5 and CD10.
- CD43 expression can occur in a subset.

How the pattern is used

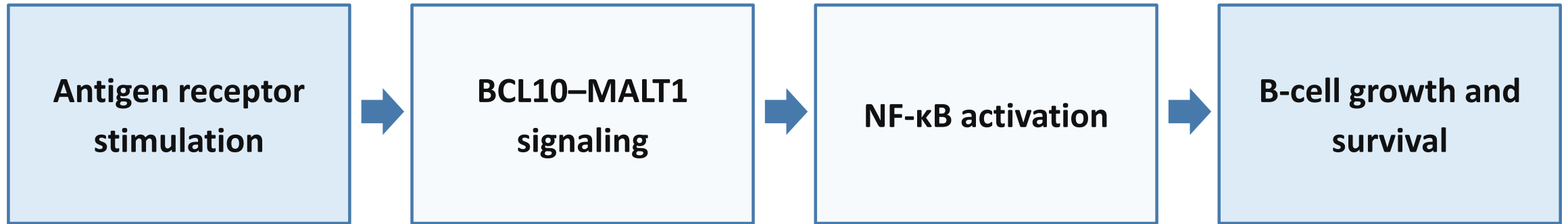
- Interpret with the architectural features and clinical setting.
- A marker pattern alone does not prove malignancy.
- Reactive and neoplastic lymphocytes require integrated assessment.

Clonality can clarify difficult gastric biopsies



Clonality is an ancillary observation, not a substitute for clinicopathologic interpretation.

NF- κ B couples immune-receptor input to B-cell survival

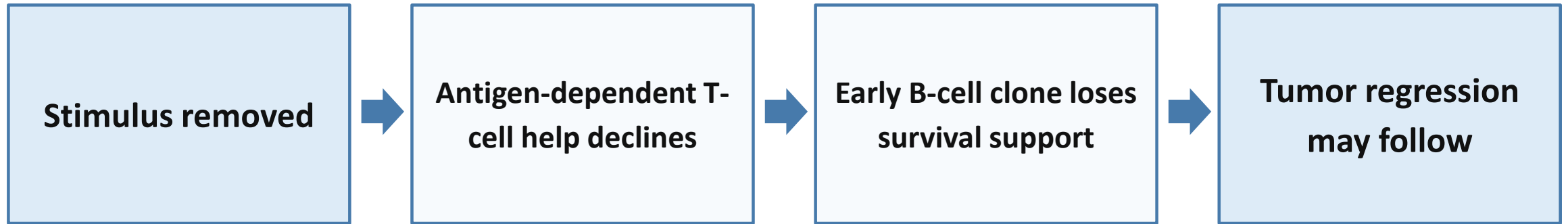


In antigen-dependent MALT lymphoma, removal of the stimulus can interrupt this pathway.

MALT lymphoma can acquire antigen-independent signaling

Genetic lesion	Principal affected product	Teaching implication
T(11;18)	API2::MALT1 fusion	Survival signaling can become autonomous
T(1;14)	BCL10 upregulation	Antigen-receptor pathway activated
T(14;18)	MALT1 upregulation	NF-κB pathway activation
T(3;14)	FOXP1 upregulation	Additional described MALT alteration

Why H. Pylori eradication may cause lymphoma regression



This response is characteristic of some gastric MALT lymphomas; It is not guaranteed.

Why eradication may fail despite successful clearance

Pathway autonomy

MALT1/BCL10-related translocations can confer reduced antigen dependence.

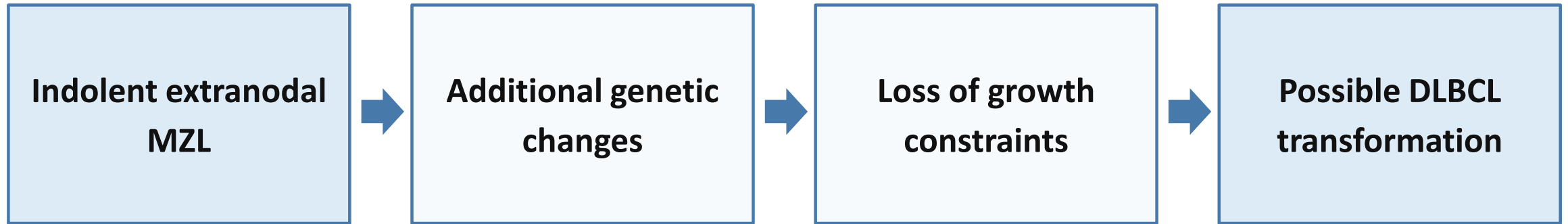
Tumor extent

Deeper wall invasion correlates with resistance.

Nodal involvement

Involved nodes correlate with resistance to eradication alone.

Clonal progression may culminate in aggressive lymphoma



Further lesions including tumor-suppressor inactivation in transformation.

Reactive H. Pylori gastritis and MALT lymphoma overlap

Assessment	Reactive inflammation	Gastric MALT lymphoma
Lymphoid infiltrate	Common with chronic gastritis	Often dense and infiltrative
Glands	Inflammatory changes possible	Lymphoepithelial lesions support suspicion
Cell population	Usually reactive / polyclonal	Clonal B-cell population may be shown
Approach	Clinical and histologic context	Morphology + phenotype ± clonality

Case: Persistent gastric symptoms and an infiltrative biopsy

Clinical vignette

A patient with chronic dyspepsia has H. Pylori gastritis and dense mucosal B-cell infiltrates. Some lymphocytes infiltrate gastric glands.

Question: Which findings favor extranodal marginal zone lymphoma over uncomplicated reactive gastritis?

Interpretation: Lymphoepithelial lesions, a compatible B-cell phenotype and—when needed—evidence of a clonal B-cell population.

Autoimmune inflammation can similarly create acquired MALT

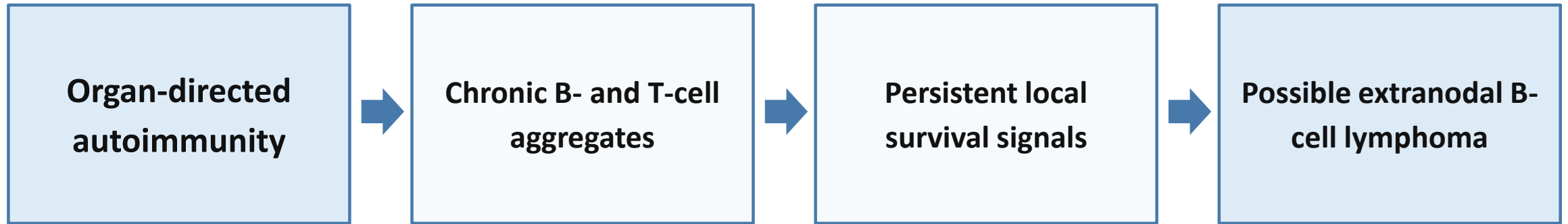
Salivary gland

- Sjögren syndrome produces persistent autoimmune inflammation.
- Extranodal marginal zone lymphoma may arise in involved salivary tissue.

Thyroid gland

- Hashimoto thyroiditis creates sustained immune infiltration.
- Extranodal marginal zone lymphoma can develop within the affected thyroid.

The autoimmune example reinforces site specificity



This is a predisposition model, not evidence that every lymphoid aggregate is premalignant.

Celiac disease creates a different lymphoma-prone compartment

Underlying immune enteropathy

- Gluten-driven response occurs in genetically susceptible hosts.
- Mucosal injury and lymphocyte recruitment persist during active disease.
- Intraepithelial cytotoxic T cells are prominent.

Lymphoma link

- Associated neoplasm is enteropathy-associated T-cell lymphoma.
- The target lineage differs from H. Pylori-linked gastric MALT lymphoma.
- The relevant tissue is small intestinal mucosa.

Celiac immune activation is anatomically organized



This is the immune injury context described in the supplied gastrointestinal chapter.

Celiac disease produces recognizable mucosal injury

Intraepithelial lymphocytes

Expanded epithelial
cytotoxic T-cell
compartment.

Crypt hyperplasia

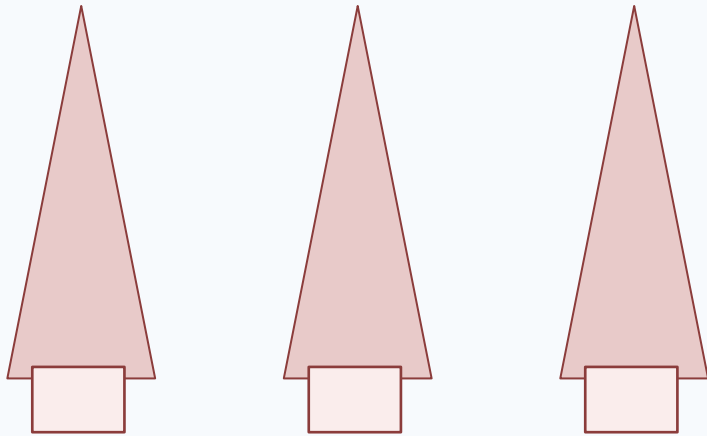
Proliferative epithelial
response to injury.

Villous atrophy

Reduced absorptive
surface in active disease.

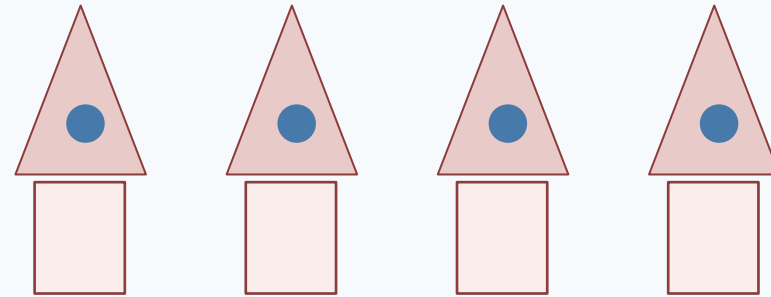
Villus, crypt and intraepithelial cell changes

Normal mucosal profile



Long villi / short crypts

Celiac-pattern injury



Short villi / longer crypts / IELs

Schematic comparison only: Normal villus/crypt organization versus celiac-pattern villous shortening and crypt hyperplasia.

Enteropathy-associated T-cell lymphoma emerges from the IEL compartment

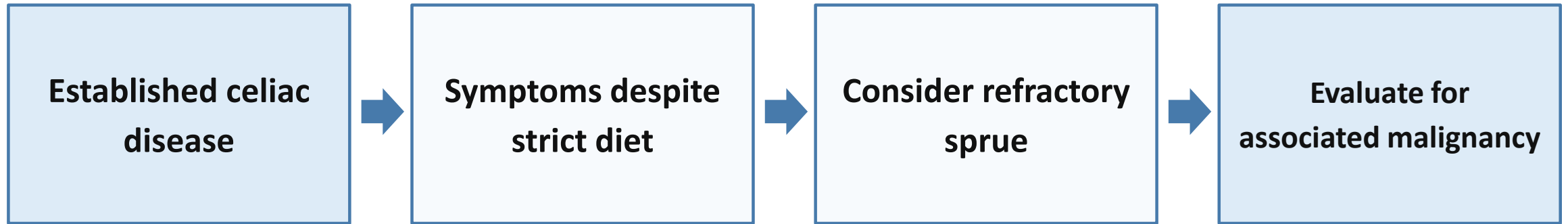
Cell of origin

- An aggressive lymphoma of intraepithelial T lymphocytes.
- Occurs with elevated frequency in celiac disease.
- Links epithelial immune injury to malignant T-cell expansion.

Clinical significance

- New symptoms can reflect refractory disease or neoplasia.
- Persistent abdominal pain, diarrhea or weight loss warrant attention.
- The diagnosis requires separate evaluation, not celiac history alone.

Persistent symptoms on a gluten-free diet are a warning



Refractory sprue as a possible precursor state to T-cell lymphoma.

Reactive enteropathy and T-cell lymphoma are not synonymous

Issue	Active celiac disease	Associated T-cell lymphoma
Process	Gluten-triggered immune injury	Neoplastic T-cell population
Biopsy context	IEL increase, crypt hyperplasia, villous atrophy	Requires evaluation for malignant lymphoid infiltration
Symptoms	Malabsorption-related symptoms	Can arise with persistent / renewed symptoms
Clinical decision	Manage and assess enteropathy	Investigate possible lymphoma or refractory sprue

Case: Clinical deterioration despite dietary exclusion

Clinical vignette

A person with established celiac disease reports progressive abdominal pain, diarrhea and weight loss despite a strict gluten-free diet.

Question: Which two processes must be considered in the differential?

Interpretation: Refractory sprue and enteropathy-associated T-cell lymphoma; Persistent symptoms alone do not establish either diagnosis.

Implant-associated lymphoma is another localized association

Named entity

- Breast implant–associated anaplastic large cell lymphoma.
- An unusual T-cell lymphoma linked to the implant setting.
- A localized chronic inflammatory milieu is considered a possible factor.

Evidence boundary

- The supplied source states an association and a possible mechanism.
- It does not establish a single definitive inflammatory pathway.
- Do not infer incidence, implant-type risk, or diagnostic criteria from this passage.

Distinguish plausible pathogenesis from confirmed findings

Claim	What the supplied Robbins text supports
Implant association	A rare T-cell lymphoma can arise in association with breast implants.
Inflammatory mechanism	Chronic inflammation is a plausible contributor.
Precise causal pathway	Not established in the cited text.
Clinical specifics	Require dedicated, independently verified sources.

Three local examples involve different lymphoid populations

Clinical setting	Principal immune compartment	Linked neoplasm
H. Pylori gastritis	Acquired mucosal B-cell aggregates	Gastric marginal zone B-cell lymphoma
Celiac disease	Intestinal intraepithelial T cells	Enteropathy-associated T-cell lymphoma
Breast implant setting	Local T-cell–associated process	Implant-associated ALCL

HIV is a contrast: Dysregulation is systemic

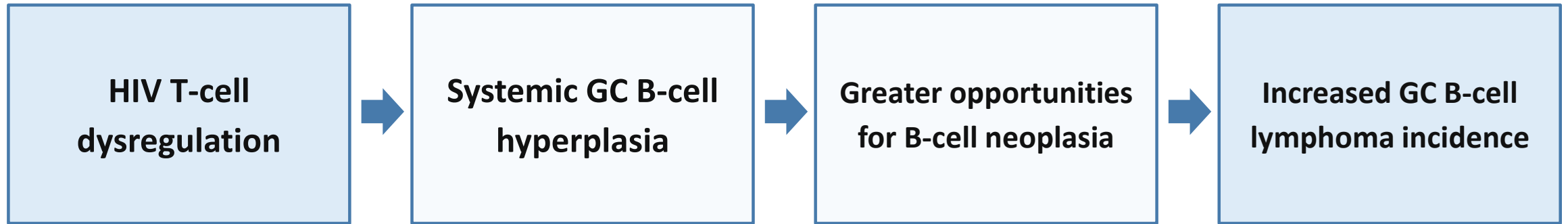
Localized inflammatory model

- Tumors tend to develop at the chronically inflamed site.
- Examples: Gastric mucosa and small intestine.
- Ongoing tissue antigenic stimulation is prominent.

HIV-associated lymphoma risk

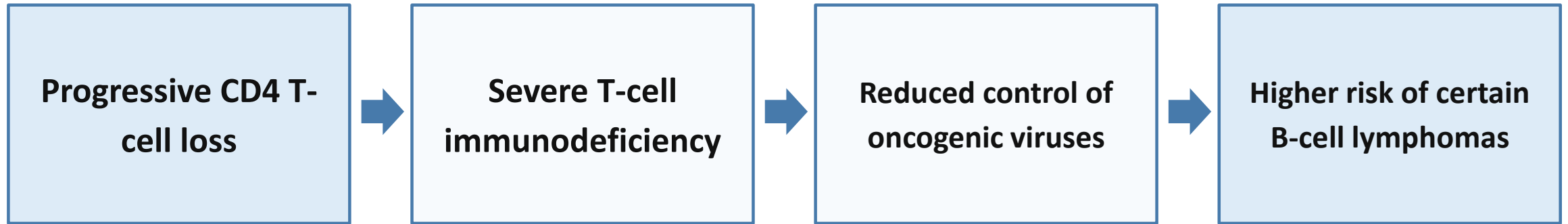
- B-cell lymphomas may arise in almost any organ.
- Early germinal-center dysregulation and later T-cell deficiency contribute.
- Virus-associated lymphomas are particularly relevant in AIDS.

Early HIV disease perturbs germinal-center B cells



This is the early-phase mechanism explicitly Chapter 13.

Advanced HIV disease adds impaired immune control



Robbins particularly links AIDS-associated lymphomas to EBV and KSHV/HHV8.

EBV and KSHV/HHV8 have distinct lymphoid associations

Epstein–Barr virus

- Present in many B-cell lymphomas in T-cell deficiency.
- Also implicated in subsets of Burkitt and Hodgkin lymphoma.
- Its frequency varies with the lymphoma setting.

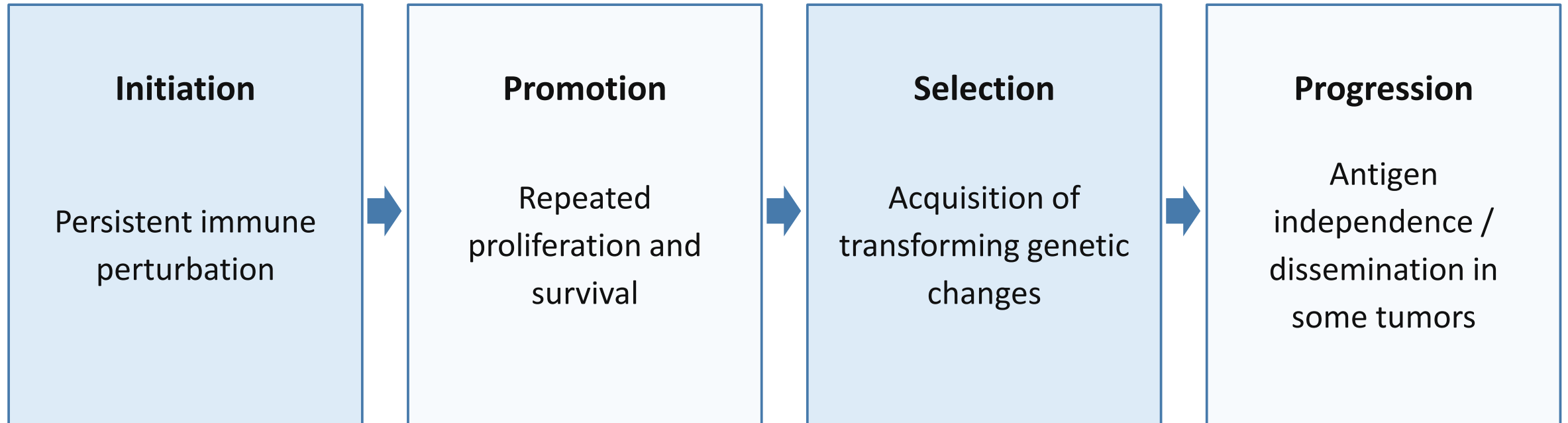
KSHV / HHV8

- Associated with an unusual effusion-forming B-cell lymphoma.
- Its importance rises in severe immune dysfunction.
- Not interchangeable with the H. Pylori antigen-driven model.

Anatomic distribution helps separate two risk patterns

Question	Localized inflammation	HIV-associated immune deficiency
Where is the driver?	At a chronically injured tissue site	Throughout immune system
Where does lymphoma arise?	Typically in or near affected tissue	Potentially at many extranodal sites
What additional biology matters?	Antigen dependence and later mutations	T-cell dysregulation and oncogenic viruses

One conceptual framework connects distinct mechanisms



B-cell and T-cell examples must not be conflated

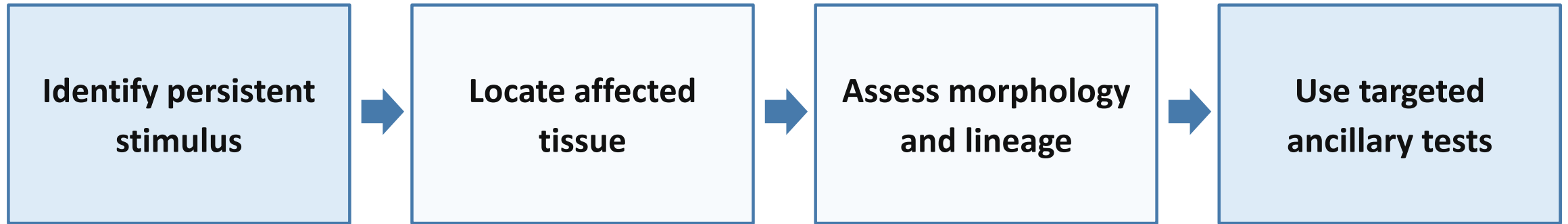
B-cell pathway

- H. Pylori-associated gastric MALT lymphoma.
- Autoimmune-associated extranodal marginal zone lymphoma.
- HIV-associated systemic B-cell lymphoma risk.

T-cell pathway

- Celiac-associated enteropathy T-cell lymphoma.
- Breast implant–associated anaplastic large cell lymphoma.
- Different lineages imply different diagnostic workups.

Diagnostic assessment begins with setting and tissue



Source-based examples include gastric B-cell clonality testing and evaluation of abnormal small-intestinal T-cell disease.

A multidisciplinary interpretation avoids shortcuts

Clinical history

Infection, immune enteropathy, autoimmunity or immune deficiency.

Pathologic pattern

Reactive architecture versus destructive or atypical infiltrate.

Ancillary evidence

Immunophenotype, clonality and relevant pathogen testing where indicated.

Case synthesis: What predicts possible eradication response?

Clinical vignette

A gastric extranodal marginal zone lymphoma is discovered with H. Pylori infection. The clinical team considers pathogen eradication as the first intervention.

Question: What underlying biologic property explains a potential regression, and what could prevent it?

Interpretation: Antigen-dependent growth can regress when the stimulus is removed; Autonomy-associated genetic lesions and greater tumor extent correlate with resistance.

Case synthesis: Widespread lymphoma risk in AIDS

Clinical vignette

A patient with advanced HIV infection develops a new extranodal mass; No localized chronic inflammatory lesion is identified at that site.

Question: Does the absence of a local *H. Pylori*-like stimulus exclude lymphomagenesis related to HIV?

Interpretation: No. Severe T-cell immunodeficiency allows B-cell lymphomas, including some EBV- and KSHV/HHV8-associated tumors, to arise in many organs.

Clinical translation: Remove drivers; Investigate autonomy

Potentially modifiable drivers

- H. Pylori clearance may remove growth input from an early gastric MALT clone.
- Recognition and management of gluten-sensitive enteropathy addresses ongoing mucosal injury.

When a clone persists

- Reassess tumor extent, tissue architecture and clonal biology.
- Antigen-independent lesions explain why trigger removal is not uniformly curative.
- Persistent or new symptoms require appropriate evaluation.

Integrated concepts to retain

- Localized, persistent immune reactions may predispose to lymphomas arising within the affected tissue.
- Inflammatory proliferation and mutations cooperate; Neither chronic inflammation nor clonality alone defines every outcome.
- Early gastric MALT lymphoma may remain antigen-dependent; BCL10/MALT1-linked lesions can confer autonomy.
- Celiac disease predisposes to intestinal T-cell lymphoma, whereas HIV-associated risk reflects systemic immune dysregulation.

Primary textbook sources

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 13: White cell neoplasia and marginal zone lymphomas.

Chapter 3: Chronic inflammation and morphologic features.

Chapter 7: Acquired cancer predisposition and inflammation-associated carcinogenesis.

Chapter 17: Gastric MALT lymphoma and celiac disease.

Chapter 23: Breast implant–associated anaplastic large cell lymphoma.