Pathology - Topic 35 - Eye

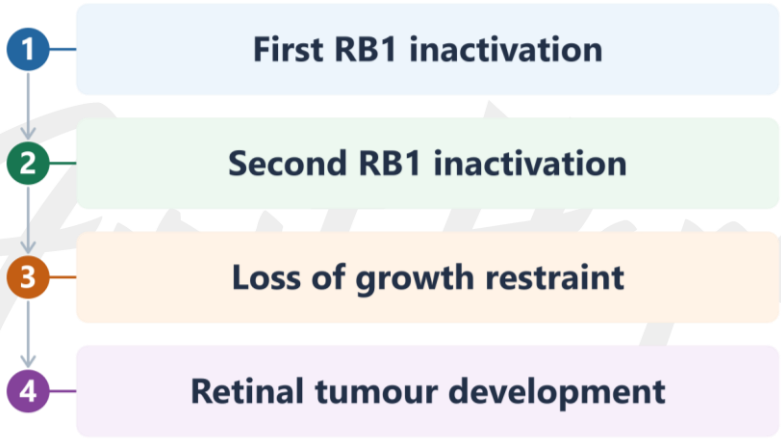
Retinoblastoma

- Retinoblastoma is a malignant embryonal tumour of the developing retina.

Origin and Clinical Importance

- It mainly affects young children and can threaten vision, the eye and life if it spreads beyond the globe.
- A child may have one tumour in one eye or multiple tumours involving one or both eyes.
- The pattern of disease provides clues to inherited susceptibility but does not replace genetic assessment.
    - Early recognition often permits a more favourable outcome because disease confined to the eye differs greatly from extraocular disease.

RB1 and the Two-Hit Mechanism



RB1 Location and Cell-cycle Control

- The **RB1** tumour-suppressor gene is located on chromosome 13q14.
    - Its protein helps restrain progression from the G1 phase into the DNA-synthesis phase of the cell cycle.
- The active RB protein restrains E2F transcription factors, linking cell-cycle progression to the G1–S checkpoint.

Loss of Function and Two Inactivating Hits

- Loss of functional RB1 in a susceptible retinal cell removes an important growth-control mechanism.
- In the classical model, both gene copies must become functionally inactivated.
    - The two inactivating events are called two hits.
    - Loss of heterozygosity, deletion, sequence alteration and promoter-related silencing are possible routes to loss of RB1 function; the two hits need not be identical molecular events.

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Genetic Patterns of Retinoblastoma

1. Heritable Retinoblastoma

Constitutional Predisposition and Early Tumours

- In heritable disease, a pathogenic RB1 variant is present constitutionally, often in many body cells.
- A second event in a developing retinal cell can then initiate tumour formation.
- Because many retinal cells already carry the first alteration, multiple tumours and bilateral disease are more likely.
- Presentation is often earlier than in non-heritable disease.

Inheritance, New Variants and Family History

- A constitutional variant may be inherited from an affected parent or arise newly.
- Absence of a family history therefore does not exclude heritable retinoblastoma.

Dominant Predisposition, Penetrance and Mosaicism

- The predisposition is transmitted in an autosomal dominant manner, although tumour formation still requires loss of both functional copies within the susceptible cell.
- Penetrance and expression vary with the variant and mosaicism.
- A carrier's clinical appearance alone cannot define the risk for every relative.

Family and Germline Implications

- A person with a constitutional heterozygous pathogenic RB1 variant can transmit that variant to approximately half of offspring, although penetrance and severity depend on the variant and mosaicism.
- Genetic assessment therefore includes both tumour susceptibility and reproductive implications, even when the child is the first recognised affected family member.

2. Non-Heritable and Mosaic Disease

Usual Somatic Mechanism

- In most non-heritable cases, both RB1-inactivating events occur within one retinal cell lineage.
- The disease is therefore more often unilateral and unifocal.
- A proportion of unilateral cases still carry a constitutional variant, so laterality alone cannot establish the genetic category.

Mosaicism and Molecular Exceptions

- Mosaicism means that a pathogenic variant is present in only a proportion of cells.
- A blood test can have limitations when low-level or tissue-limited mosaicism is present.

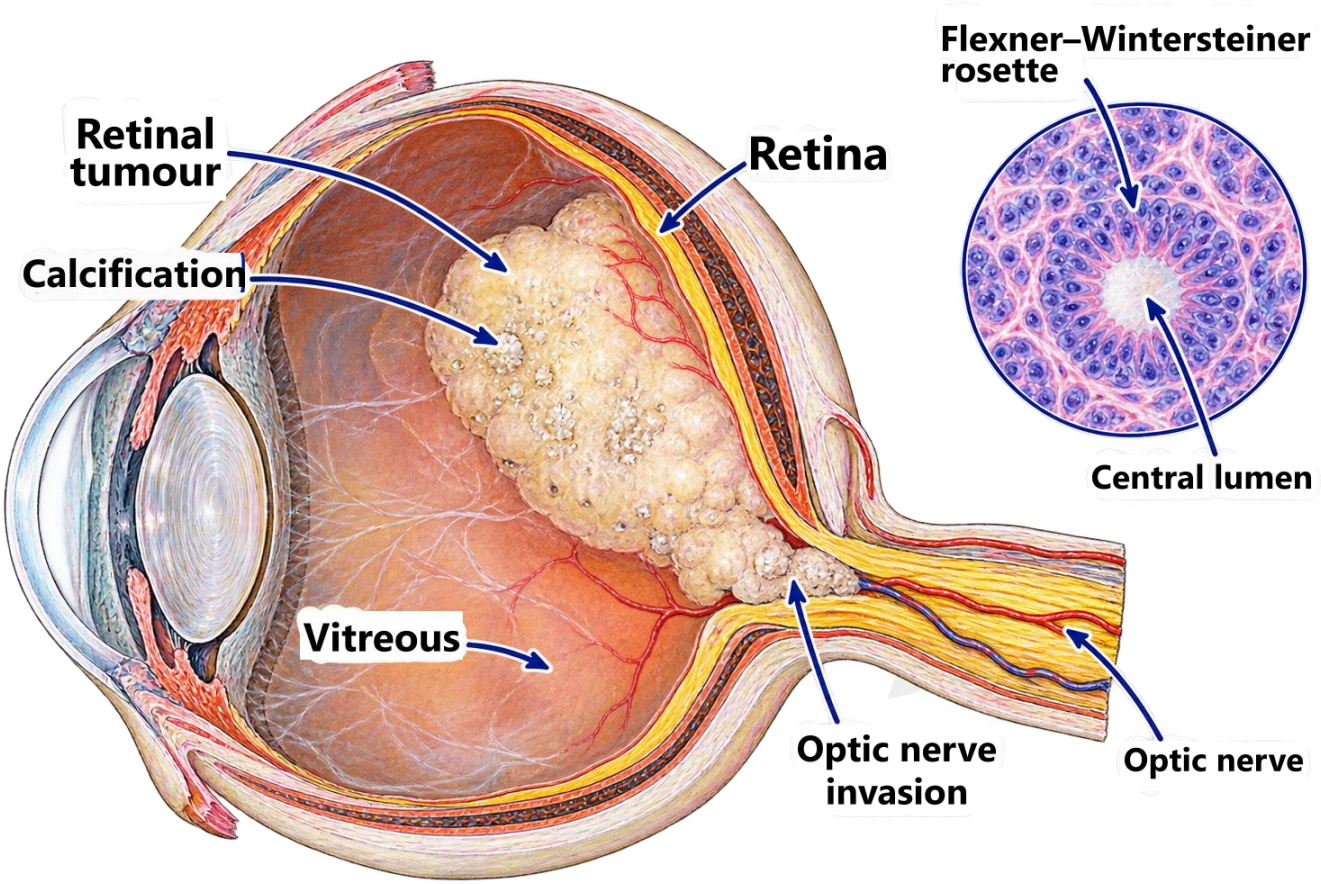
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- Rare retinoblastomas involve alternative molecular mechanisms, including MYCN amplification without the usual biallelic RB1 pattern.
- These exceptions do not invalidate the two-hit model for the great majority of cases.

Interpreting a Negative Blood Result

- A negative blood assay may leave residual uncertainty if assay sensitivity or mosaicism limits detection, so tumour testing and the clinical phenotype can contribute to classification.

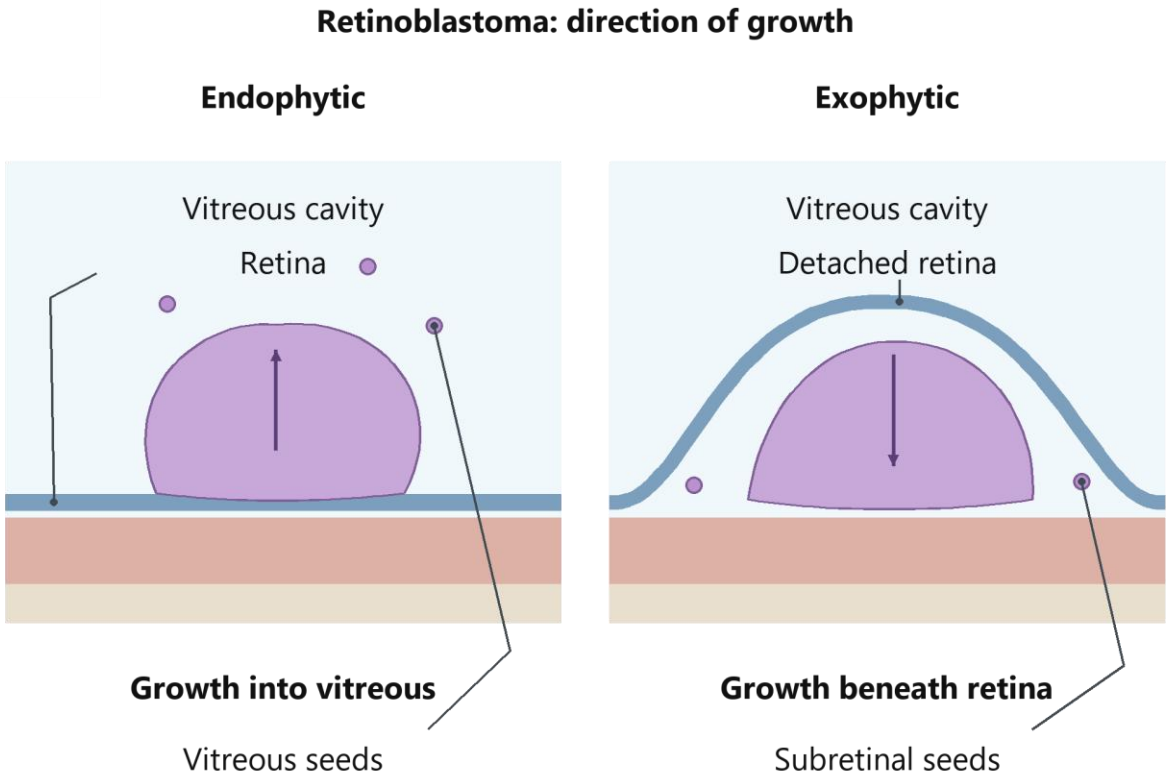
Gross Growth Patterns



Retinoblastoma within the eye and a Flexner–Wintersteiner rosette

- The tumour commonly appears as a cream-white retinal mass with areas of necrosis and calcification.
- It may grow towards the vitreous cavity, beneath the retina or in both directions.

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Either pattern may occur with the other; the drawing shows simplified examples

Endophytic and exophytic retinoblastoma grow towards different retinal compartments

1. Endophytic Growth

- Endophytic growth projects towards the vitreous cavity.
- Tumour cells can detach and form vitreous seeds.
    - Vitreous seeding affects local disease assessment because it represents tumour outside the main retinal mass but still within the eye.

2. Exophytic Growth

- Exophytic growth extends beneath the retina and can produce retinal detachment.
- Tumour cells may seed the subretinal space.
    - A detached retina can further reduce vision and obscure the original site of the lesion.

3. Diffuse Infiltrating Growth

- An uncommon diffuse pattern spreads through the retina without a dominant obvious mass.
- It can resemble inflammatory eye disease and delay recognition.

Microscopic Features

Small Blue Cells, Necrosis and Calcification

- The tumour consists of small cells with scant cytoplasm, dark nuclei and a high nuclear-to-cytoplasmic ratio.

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