LOSS OF RhD ANTIGENS

How A Positive Became A Negative

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CASE STUDY – A.M.

CLINICAL

• 73 year old female
• Known essential thrombocytosis (ET)
• Presented with worsening headache and papilloedema
• Extensive thromboses despite warfarin therapy
• Bone Marrow Trephine:
  – consistent with known essential thrombocytosis
  – no evidence of transformation to myelofibrosis
• Bone Marrow Cytogenetics:
  – no abnormalities at <300 band resolution
  – normal 46,XX[40] karyotype
• Diagnosed with cerebral venous sinus thrombosis
TRANSFUSION

- Grouped as A Positive at Nowra, 2011.
- Grouped as A Negative at Wollongong, 2012.
- Antibody screen consistently ‘Nil Detected’.
- Clinical notes did not provide any obvious explanation for the discrepancy.
- Collection error ruled out by two recollects.
- Tube RhD and weak-D typing confirmed RhD Negative (rr) result.
- A.M. confirmed to be the same patient that had been previously tested in Nowra
- A.M.’s group changed to A Negative in Cerner.
1. Loss of Rh Antigen Associated With Acquired Rh Antibodies and a Chromosome Translocation in a Patient With Myeloid Metaplasia

2. Shift from Rh-positive to Rh-negative phenotype caused by a somatic mutation within the RHD gene in a patient with CML

3. Mosaicism due to myeloid lineage-restricted loss of heterozygosity as a cause of spontaneous Rh phenotype splitting
CONCLUSIONS

• In Caucasians, the deletion of the whole RHD gene is the usual basis for the RhD Negative phenotype, whilst RhD Positive individuals may be homozygous or heterozygous.

• A clear relationship was observed between haematological diseases and Rh antigen loss.

• The main reason for the loss of Rh antigens, after excluding transfusions, transplants, and inherited chimerism, was a loss of RHD heterozygosity.

• This was found to occur in three main ways:
  – the recombination of genetic material in chromosome 1 and the subsequent proliferation of abnormal stem cell clones (mosaicism) (most common).
  – a single nucleotide deletion in the RHD gene.
  – complete deletion of a stretch of chromosome 1, including the RH locus (rare).
• Flow cytometry can be used to determine the proportion of RhD Positive to RhD Negative red blood cells
• FISH analysis would enable recombinations of chromosome 1, and particularly the \( \textit{RHD}/\textit{RHCE} \) gene, to be visualised.
• Microsatellite analysis of the \( \textit{RH} \) loci would highlight any nucleotide deletions, insertions, substitutions or duplications, and could also be used to provide the Rh genotype of the patient.
WHAT ABOUT A.M.?

• Crossmatching of RhD Negative red blood cells was the safest option.
• No further testing was performed to identify the cause of the RhD antigen loss
• Recent grouping of A.M. has identified weak RhD reactions. Is she returning to her A Positive phenotype, or are we just seeing an increase in the number of RhD Positive cells back up to detectable level?
• The remission of myeloproliferative disorders has been suggested to lead to the return of Rh antigens, however no improvement in A.M.’s ET has been recorded.
• Ongoing monitoring of A.M. may involve the careful observation of her blood film morphology and flow cytometry markers for signs of remission or, alternatively, transformation to myelofibrosis.
REFERENCES


• Cherif-Zahar, B et al. Shift from Rh-positive to Rh-negative phenotype caused by a somatic mutation within the RHD gene in a patient with CML. BJH. Vol. 102, pp. 1263-1270, 1998.

QUESTIONS?