COVID plus CVID: A Recipe for Pure Red Cell Aplasia

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Common Variable Immunodeficiency: CVID

- A group of hypogammaglobulinemia syndromes due to genetic mutation, most frequently in the TNFRSF13B gene, which codes for the TACI protein.
- TACI (Transmembrane activator and CAML interactor) protein is involved in T-cell independent B-Cell antibody responses and B-cell proliferation.
- Defective immunoglobulin production due to compromised B-cell differentiation.
- Causes recurrent bacterial infections in children and adults due to reduced concentrations of serum IgG, commonly sinopulmonary.
- Common pathogens include *Streptococccus pneumoniae*, *Haemophilus influenzae*, and atypicals such as *Mycoplasma*.
- Over a quarter of patients with CVID also suffer from other autoimmune conditions such as rheumatoid arthritis, immune thrombocytopenia, and autoimmune hemolytic anemia.
- IVIG is the mainstay of treatment for individuals with profound impairment of antibody production.
- Pure red cell aplasia is a rare but reported phenomenon in CVID.

Case Summary

We describe a case of pure red cell aplasia in a patient diagnosed with CVID after an infection with COVID-19:

- A 55 year old male with history of CVID who was maintained on monthly IVIG presented to Reading Hospital complaining of dyspnea after a diagnosis of COVID-19 infection two weeks prior.
- Hemoglobin on presentation was 7g/dL from a baseline of 11.7g/dL. He experienced worsening anemia with hemoglobin dropping to 6 g/dL in the absence of other cytopenias, which persisted for 3 months after COVID-19.
- There was no evidence of bleeding or hemolytic anemia. Reticulocyte count was severely suppressed at 0 to 0.010%.
- Other causes of PRCA were evaluated and ruled out including LGL, thymoma, parvovirus, nutritional deficiency, medication, and hematologic malignancy.
- Ferritin was found to be elevated at 1,346ng/DL with an iron saturation of 94%, suggesting ineffective erythropoiesis.
- Bone marrow biopsy was performed and revealed pure red cell aplasia with markedly increased M:E ratio, near complete absence of erythroid progenitors with scant proerythroblasts in maturation arrest.
- The patient had continued IVIG therapy during this time, but his dose was increased to 90g from 45g. His anemia remained unchanged.
- Therapy with cyclosporine A and prednisone was initiated in June 2021. CsA was dosed at 3mg/kg BID and prednisone was started at 30mg daily.
- Robust erythrocyte response was noted after CsA/Prednisone therapy, and the patient's hemoglobin returned to baseline (~12.0g/dL) after about 6 months of therapy.
- Prednisone was tapered off and CsA was discontinued after 10 total months of therapy. The patient continued monthly IVIG at 45g/dose.
- Hemoglobin has remained stable after discontinuation of cyclosporine A.

Hypogammaglobulinemia in CVID

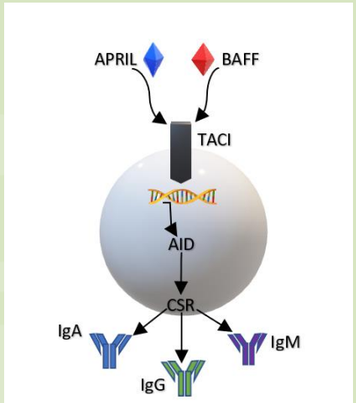

Fig. 1 The role of TACI in B-Cell response to pathogens
TACI is activated by B-cell activating factor (BAFF) and proliferation inducing ligand (APRIL) which subsequently increases AID transcript levels, inducing class switch recombination which results in isotype switch to IgA and IgG. Mutations in the gene coding for TACI is a common finding in CVID.

PRCA Findings on Bone Marrow Biopsy

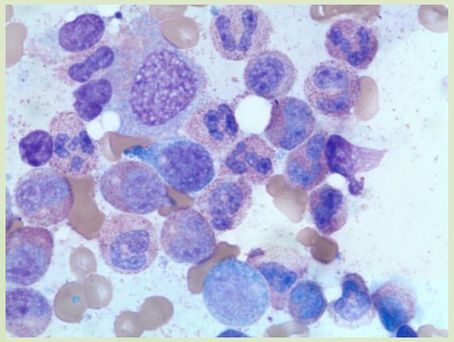

Fig. 2 Arrested Erythrocyte Precursors in Bone Marrow
The patient's bone marrow was cellular but demonstrated pure red cell aplasia with few erythrocyte precursors showing an arrest in maturation.

100x oil immersion

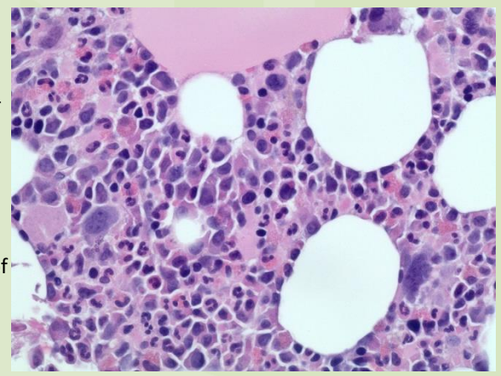

Fig. 3 Pure Red Cell Aplasia
Bone marrow biopsy showed only 2.8% erythrocyte precursor cells. M:E ratio was markedly increased. Myeloid activity matured to completion, while identified erythroid elements consisted of scattered proerythroblasts with absence of maturing forms.

40x magnification

Acknowledgements

We would like to thank Dr. Sharon Swierczynski, hematopathologist at Reading Hospital, for providing pathology images for this presentation.

Discussion

Pure red cell aplasia has been reported in CVID patients and was treated successfully in this patient with immunosuppression therapy (cyclosporine A/prednisone).

- PRCA has been described in CVID patients with or without thymoma.
- The pathophysiology suggests multifactorial effects on erythrocyte progenitor cells resulting in erythrocyte aplasia. These include:

1. **Viral or pathogenic persistence due to immunodeficiency causing marrow suppression and/or direct cytotoxicity.**
2. **Immunodeficiency may lead to the generation of auto-reactive T-cells which attack erythroid progenitors due to lack of HLA class 1 restriction.**
3. **Aberrant CTL responses due to reduced viral clearance with immunodeficiency.**

Pathophysiology of PRCA in CVID

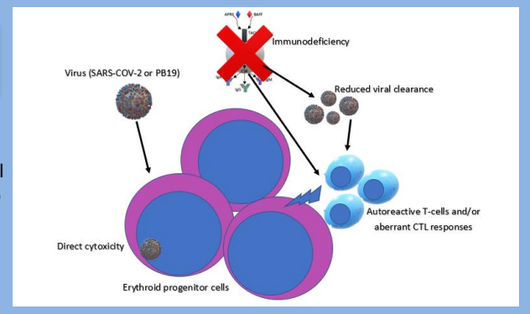

Fig. 4 Multifactorial cytotoxicity in CVID
Immunodeficiency and viral pathogenicity contribute to toxic effects on erythroid progenitor cells.

- Unusual clonal gammopathies have been reported in patients infected with SARS-COV-2 and is thought to be due to elevated levels of IL-6 causing transitory plasma cell dyscrasia and other cytopenias, including anemia.
- In this individual, persistent viral mediated marrow toxicity combined with CVID autoimmune related erythroblastopenia were likely multifactorial contributors to PRCA.
- The use of cyclosporine A and prednisone provided necessary immunosuppression due to autoimmune effects against erythroid progenitor cells and allowed for recovery of erythrocyte cell lines.
- IVIG was likely ineffective due to lack of effect on T-cell mediated autoimmune disease, one proposed mechanism of CVID related PRCA.

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