A Patient With Mouth Ulcers, Large Red Blood Cells and Recurrent Infection

Nikhil Holla
Karthik Venkataraman
Vijay Damarla, MBBS
Guha Krishnaswamy, M.D., FACP, FCCP, FAAAAI, FACAAC, CC-D

Division of Allergy and Clinical Immunology
Department of Medicine

Disclaimer

NEITHER THE PUBLISHER NOR THE AUTHORS ASSUME ANY LIABILITY FOR ANY INJURY AND OR DAMAGE TO PERSONS OR PROPERTY ARISING FROM THIS WEBSITE AND ITS CONTENT.

Take a disease or condition and understand the molecular aspects

Bedside To Bench

Case Report
Patient Interview
Clinical Presentation
Caucasian Female Patient Presenting with:

- Areas of necrotic ulceration of mouth and tongue over several years
  - This is accompanied by severe burning pain and inability to sleep or eat
  - Nonspecific arthralgia and photosensitive eruption over face?
  - Cycles last 3 weeks or more
  - Severe episodes over the last year

Significant Other Diagnoses

- Myofascial pain syndrome (Cymbalta)
- Hypertension
- Anemia: Requiring iron infusions
- Headaches (Mixed functional/vascular)
- Von Willebrand disease
- OBGYN: Endometriosis with cyst in left ovary
  - Pre-eclampsia
  - S/p hysterectomy and left oophorectomy
- Recurrent infections
  - Staphylococcal face infections (hospitalized)
  - Recurrent sinusitis and bronchitis

Family History

- Cluster of immunoregulatory disease
  - Aunt – CVID
  - 2 cousins with IgA deficiency
  - 3 cousins with Diabetes mellitus
  - Nephew with leukemia and IgA deficiency

The patient’s peripheral smear shown below demonstrates:

1. Eosinophilia
2. Megablast
3. Macropolycyte
4. Neutrophil precursor
5. Megakaryocyte

Digital image of patient’s Peripheral smear obtained by Dr Youngberg
### Initial Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
<th>Test</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136 mmol/L</td>
<td>134-145</td>
<td>WBC</td>
<td>6.8 Thou/µL</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6 mmol/L</td>
<td>3.6-5.0</td>
<td>LY%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>9</td>
<td>7-16</td>
<td>MO%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Glucose</td>
<td>126 mg/dL</td>
<td>65-110</td>
<td>CRP</td>
<td>71.1%</td>
</tr>
<tr>
<td>BUN</td>
<td>5 mg/dL</td>
<td>7-17</td>
<td>RBC</td>
<td>3.91 mW/µL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7 mg/dL</td>
<td>0.7-1.2</td>
<td>HGB</td>
<td>13.7 g/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.1 mg/dL</td>
<td>8.2-10.3</td>
<td>HCT</td>
<td>40%</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.4 g/dL</td>
<td>3.5-5.0</td>
<td>MCV</td>
<td>101.7 fL</td>
</tr>
<tr>
<td>TSH</td>
<td>3.13 µIU/mL</td>
<td>0.4-4.0</td>
<td>MCH</td>
<td>35 pg</td>
</tr>
<tr>
<td>ALT</td>
<td>7 U/L</td>
<td>7-52</td>
<td>MCHC</td>
<td>35 g/dL</td>
</tr>
<tr>
<td>AST</td>
<td>11 U/L</td>
<td>13-39</td>
<td>RDW</td>
<td>13.4%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.5 mg/dL</td>
<td>0.2-1.3</td>
<td>Platelets</td>
<td>189 Thou/µL</td>
</tr>
<tr>
<td>Protein</td>
<td>6.1 g/dL</td>
<td>6.4-8.9</td>
<td>MPV</td>
<td>7.7 fL</td>
</tr>
</tbody>
</table>

### Types Of Aphthous Ulcers (RAS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Major</th>
<th>Minor</th>
<th>^Herpetiform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10%</td>
<td>85%</td>
<td>5%</td>
</tr>
<tr>
<td>Size</td>
<td>&gt;1.0 cm large</td>
<td>&lt;1.0 cm</td>
<td>2 mm shallow ulcers</td>
</tr>
<tr>
<td>Location</td>
<td>Posterior oral cavity</td>
<td>Nonkeratinized</td>
<td>Keratinized and nonkeratinized</td>
</tr>
<tr>
<td>Pain</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Healing</td>
<td>6 weeks</td>
<td>10 days</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>HIV</td>
<td>+++</td>
<td>+/-</td>
<td>---</td>
</tr>
</tbody>
</table>

* Keratinized stratified squamous: Dorsum tongue, hard palate and gingiva
^ Herpetic infections have usual prodrome and vesicle formation, absent in RAS

### A Patient with multiple 1 cm ulcers over the oropharynx and associated odynophagia has:

1. Minor apathous ulcers
2. Herpetiform apthous ulcers
3. Major apthous ulcers
4. Vincent’s angina

### The Diagnosis Is:

1. Staphylococcal infection
2. Glucagonoma Syndrome
3. Atrophic Glossitis
4. Migratory Glossitis
5. Lemierre’s syndrome
Glossitis And/Or Tongue Ulcer Are An Unlikely Feature of:

1. Plummer-Vinson Syndrome
2. Ataxia Telangiectasia
3. Iverslund-Grasbeck syndrome
4. PFAPA syndrome
5. Food-Cobalamin malabsorption syndrome

Differential Diagnosis: Glossitis

<table>
<thead>
<tr>
<th>Psychological stress</th>
<th>Glossitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic/iatrogenic injury</td>
<td>Crohn’s disease/ulcerative colitis</td>
</tr>
<tr>
<td>Associated systemic diseases/conditions/syndromes</td>
<td>Behçet’s disease, SLE, Reiter’s</td>
</tr>
<tr>
<td></td>
<td>PFAPA syndrome</td>
</tr>
<tr>
<td></td>
<td>Malabsorption/gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>HIV disease</td>
<td>Deficiency: B12, Folate, Fe</td>
</tr>
<tr>
<td></td>
<td>Sweet’s syndrome (acute neutrophilic dermatosis)</td>
</tr>
<tr>
<td>Foods</td>
<td>Chocolate</td>
</tr>
<tr>
<td></td>
<td>Tomatoes</td>
</tr>
<tr>
<td></td>
<td>Walnuts, hazelnuts, Brazil nuts</td>
</tr>
<tr>
<td>Menstrual cycle</td>
<td></td>
</tr>
</tbody>
</table>

This patient presented with a persistent erythematous area of the tongue shown below. He denies pain or odynophagia. The diagnosis is:

1. Geographic Tongue
2. Anthracycline intoxication
3. Lead poisoning
4. Median rhomboid glossitis
5. Tertiary Syphilis

Median Rhomboid Glossitis

- Median rhomboid glossitis--also known as central papillary atrophy and posterior midline atrophic candidiasis
- Rhomboid atrophy of filiform papillae due to candidal infection
- It occurs in as many as 1% of adults and is often asymptomatic
- Clinically, median rhomboid glossitis manifests as a well-delineated erythematous area located along the midline posterior dorsal tongue just anterior to the vallate papillae
This 13 year old diabetic presents with a painful tongue of three weeks duration. The observed plaques can be removed with a tongue blade. The diagnosis is:

1. Mucocutaneous Candidiasis
2. Acute pseudomembranous candidiasis
3. Leukoplakia
4. Oral hairy leukoplakia
5. Migratory glossitis

Oropharyngeal Candidiasis

- Acute candidiasis
  - Acute pseudomembranous candidiasis (Thrush)
  - Acute atrophic (erythematous) candidiasis
    - Smokers, HIV infection
- Chronic candidiasis
  - Chronic hyperplastic candidiasis
    - Candidal leukoplakia
    - CMC-IFN gamma/CMI defect
    - Candidal endocrinopathy syndrome
  - Denture induced candidiasis
    - Chronic atrophic erythematous candidiasis
  - Median rhomboid glossitis
- Angular cheilitis (stomatitis)

This Patient With a Raw Tongue Probably Has:

1. Atrophic glossitis
2. Hunter’s Glossitis
3. Plummer-Vinson Syndrome
4. Lingua Villosa Nigra
5. Median Rhomboid Glossitis

The Diagnosis is:

1. Oral Hairy Leukoplakia
2. Vincent’s Angina
3. Lemierre’s Syndrome
4. Migratory Glossitis
5. Malignant Glossitis
Oral Hairy Leukoplakia

Eponym Moller-Hunter Syndrome Includes All the Following Except:
1. Glossopyrosis
2. Glossodynia
3. Uveitis
4. Parietal cell atrophy
5. Macroovalocytes

Certain Confirmatory Tests Were Done

Immunological Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>789</td>
<td>600-1600 mg/dL</td>
</tr>
<tr>
<td>IgA</td>
<td>&lt;7/&lt;5</td>
<td>68-276 mg/dL</td>
</tr>
<tr>
<td>IgM</td>
<td>54</td>
<td>45-250 mg/dL</td>
</tr>
<tr>
<td>IgE</td>
<td>&lt;2</td>
<td>13.8-128 U/mL</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>IgG1</td>
<td>456</td>
<td>240-1118 mg/dL</td>
</tr>
<tr>
<td>IgG2</td>
<td>256</td>
<td>124-549 mg/dL</td>
</tr>
<tr>
<td>IgG3</td>
<td>64</td>
<td>21-134 mg/dL</td>
</tr>
<tr>
<td>IgG4</td>
<td>&lt;1</td>
<td>7.89 mg/dL</td>
</tr>
<tr>
<td>Pneumococcal IgG response</td>
<td>Robust 14/14 serotypes</td>
<td>&gt;1 U/mL</td>
</tr>
<tr>
<td>Tetanus antibody</td>
<td>3.7</td>
<td>&gt;0.1 U/mL</td>
</tr>
<tr>
<td>Diphtheria antibody</td>
<td>2.82</td>
<td>&gt;0.1 Ug/mL</td>
</tr>
<tr>
<td>CH50</td>
<td>74</td>
<td>50-144 CAE units</td>
</tr>
</tbody>
</table>
Tests For Macrocytosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum B12</td>
<td>&lt;150 (L)</td>
<td>193-982 pg/mL</td>
</tr>
<tr>
<td>RBC folate</td>
<td>339 ng/mL</td>
<td>280-903 ng/mL</td>
</tr>
<tr>
<td>Vitamin D (25 OH)</td>
<td>24 (L)</td>
<td>25-80 U/mL</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>3.2 (L)</td>
<td>5-30 ng/mL</td>
</tr>
<tr>
<td>ANA/anti-DNA</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>RF/CCP/SSA/SSB</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Homocystine</td>
<td>32 (H)</td>
<td>&lt;1.5 mmol/L</td>
</tr>
<tr>
<td>Methylmalonic Acid</td>
<td>2385 (H)</td>
<td>73-375 mmol/L</td>
</tr>
<tr>
<td>Serum Gastrin</td>
<td>335</td>
<td>&lt;100 pg/mL</td>
</tr>
<tr>
<td>H Pylori antibody</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Antibody to IF</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Antibody to Parietal cells</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Celiac disease panel</td>
<td>Neg</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Diagnoses:
Linear glossitis/Hunter-Moeller syndrome
Pernicious anemia with atrophic gastritis
Vitamin D and B6 deficiency (mild)
Selective IgA deficiency with good functional response to vaccination
Selective IgE deficiency
IgG subclass deficiency

Immune Dysregulation in Immune Deficiency

Healthy
Infection
S-IgAD
Neoplasia
Allergy
Autoimmunity
+VA
+CTD
+IBD
Polyglandular Autoimmune syndrome
Overlap autoimmunity

B12 Deficiency: Clinical and Molecular Update

Nikhil Holla
Vijay Damarla
Guha Krishnaswamy, M.D.
**Epidemiology**

- Prevalence ranges from 5-60%, averaging 20%
- Framingham estimates prevalence of 12% in the elderly
- Using stringent criteria, French group estimates overall prevalence of ~5%

**Imerslund-Grasbeck syndrome is characterized by all the following except:**

1. Deafness
2. Proteinuria
3. Mutation of cubilin gene
4. Mutation of amnionless gene
5. Defective ileal receptor for B12-intrinsic factor complex

**B12 Deficiency: Etiology**

- Pernicious anemia
  - Biermer’s disease
  - 20-50% of B12 deficiency
  - Anti-IF antibody sensitivity 50%, specificity >90%
  - Anti-parietal cell antibody: sensitivity 90%, specificity 50%
  - Hypergastrinemia has sensitivity of >80% and specificity <50%
  - +ve Schilling test confirms dx (specificity >99%)

- Hereditary disorders
  - Imerslund-Grasbeck syndrome
  - Selective B12 malabsorption
  - Appears in childhood
  - Failure to thrive
  - Mild proteinuria
  - Appears at 4 months of age
  - Mutation of cubilin (CUBN) on chromosome 10
  - Mutation of amnionless (AMN) on chromosome 14
  - Defective ileal receptor for B12-IF complex on Ileum
  - TCII deficiency
  - Appears at birth

- Specific Disorders
  - Hereditary disorders
    - Imerslund-Grasbeck syndrome
    - Selective B12 malabsorption
    - Appears in childhood
    - Failure to thrive
    - Mild proteinuria
    - Appears at 4 months of age
    - Mutation of cubilin (CUBN) on chromosome 10
    - Mutation of amnionless (AMN) on chromosome 14
    - Defective ileal receptor for B12-IF complex on Ileum
    - TCII deficiency
    - Appears at birth
**B12 deficiency is characterized by:**

1. Elevation of homocysteine only
2. Elevation of both homocysteine and methylmalonic acid
3. Low plasma uric acid level
4. Mutation in tetrahydrofolate reductase
5. All of the above

**Metabolic Pathways and B12/Folate**

- Elevated MMA and homocysteine are seen in B12 deficiency; elevated homocysteine can be seen in folate deficiency; hyperhomocysteinemia can lead to myocardial infarction and stroke. These confirm diagnosis of deficiency.

---

**A Patient with megaloblastic anemia, diarrhea following SUSHI ingestion and the following finding in the stool has:**

1. Guinea worm infection
2. Diphyllobotrium Latum infection
3. Schistosomia Hematobium infection
4. Trichinell spiralis infection
5. Ascaris Lumbricoides infection

---

**D. Latum Infection**

- Person can be infected by eating raw, lightly cooked, under-processed freshwater or certain migratory species of salmon, perch, pike, pickerel, and turbot
- The popularity of eating raw fish dishes, such as Japanese sushi and sashimi, helps to spread this disease
- Cooks who sample their fish dishes before they are properly cooked put themselves at risk of being infected
- Fish tapeworms are found wherever humans, bears, and other fish-eating mammals defecate in the same lakes and streams from which this fish are obtained
- Nausea, diarrhea, abdominal distension, weight loss and B12/folate deficiency may result though many are asymptomatic

---
### Diagnosis Of Cobalamin Deficiency

- Serum cobalamin levels <150 pmol/l
  - Plus clinical features and/or hematological anomalies related to cobalamin deficiency
- Serum cobalamin levels <150 pmol/l (<200 pg/ml) on two separate occasions
- Serum cobalamin levels <150 pmol/l and total serum homocysteine levels >13 mmol/l or methylmalonic acid levels >0.4 mmol/l
  - In the absence of renal failure and/or severe folate and vitamin B6 deficiencies
- Low serum holo-transcobalamin levels <35 pmol/l

### Diagnosis Of Cobalamin Deficiency

- MCV > 100 fl (usually >110)
- PBS: anisocytosis, macro-ovalocytes, hypersegmented neutrophils, basophilic stipling, nucleated RBC, pancytopenia in severe cases
- Bone marrow: Marked erythroid hyperplasia with megaloblastic changes
- Schilling test (ND now due to reimbursement and IF-related safety issues)

---

### Anemia With Normal MCV in B12 Deficiency Represents:

1. Bone marrow dysfunction
2. Dimorphic anemia
3. Splenomegaly
4. Infection

### Typical Features of B12 deficiency include all the following except:

1. Pancytopenia
2. Gastric carcinoma
3. Psychosis
4. Diplopia
5. Sensory ataxia
**Clinical features**

- **Hematology**
  - Anemia: weakness, palpitations, angina, congestive failure, systolic flow murmur
  - Hyperbilirubinemia due to high erythroid turnover in marrow
  - Purpura (rare)
- **GI Tract**
  - Sore smooth beefy red tongue
  - Glossitis (Hunter’s) – diffuse erythema and lingual atrophy
  - Glossodynia, dygeusia, xerostomia, cheilitis
  - Anorexia, weight loss, diarrhea
  - Increased frequency of gastric neoplasms
- **Neurological**
  - Sensory: peripheral nerves, posterior and lateral columns and cerebrum
    - Stages:
      - Demyelination
      - Axonal degeneration
      - Neuronal death (irreversible)
    - numbness, paresthesia (early)
    - Sphincter disturbances
    - Ataxia
    - Diminished reflexes, position and vibration senses
    - Positive Romberg and Babinski’s signs
    - Dementia, psychosis
- **CVS**
  - Stroke, MI (homocysteine)

**Mouth Ulcers**

- Linear Glossitis: Journal of the American Academy of Dermatology - Volume 60, Issue 3 (March 2009)
  - Atrophic glossitis (bald tongue) may be seen in patients with pernicious anemia, iron deficiency anemia, pellagra, and xerostomia
  - Möller-Hunter syndrome: It is characterized by glossitis, glossodynia, glossopyrosis, and altered sense of taste; B12 deficiency, associated gastric atrophy present
  - Julius Otto Ludwig Möller
  - William Hunter
One cause is the use of anticonvulsants such as dilantin.

<table>
<thead>
<tr>
<th>Useful Cobalamin Numbers</th>
<th>Normal absorption</th>
<th>Malabsorption disease (eg, PA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated daily loss/requirement</td>
<td>1 µg/day</td>
<td>2 µg/day/week</td>
</tr>
<tr>
<td>Recommended daily allowance</td>
<td>2.4 µg/day</td>
<td>Supplements are required</td>
</tr>
<tr>
<td>Amount (percentage) absorbed from a single oral dose of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 µg</td>
<td>0.56 µg (56%)</td>
<td>1.08 µg (16.5%)</td>
</tr>
<tr>
<td>10 µg</td>
<td>1.4 µg (14%)</td>
<td>1.3 µg (13%)</td>
</tr>
<tr>
<td>50 µg</td>
<td>1.9 µg (19%)</td>
<td>0.6 µg (1.2%)</td>
</tr>
<tr>
<td>100 µg</td>
<td>3.2 µg (32%)</td>
<td>0.2 µg (0.2%)</td>
</tr>
<tr>
<td>1000 µg</td>
<td>13 µg (1.3%)</td>
<td>12 µg (1.2%)</td>
</tr>
</tbody>
</table>

Amount (percentage) retained from a single injection of:
- 10 µg | 9.7 µg (97%) | Same as normal |
- 100 µg | 9.1 µg (91%) | Same as normal |
- 1000 µg | 150 µg (15%) | Same as normal |

Deficiency of cobalamin may occur if stores are inadequate, in the absence of macroscopic lesions.

**IgA Deficiency**

Kartik Venkataraman

**All the following are correct regarding IgA deficiency except:**

1. There is a higher prevalence of autoimmune disease
2. In severe deficiency, anaphylaxis to blood products is a serious complication
3. One cause is the use of anticonvulsants such as dilantin
4. Most patients are symptomatic with infections
5. Patients with associated IgG subclass deficiency are usually more symptomatic

**Treatment**

- I.M. Cyanocobalamin 1000µg/day x 1 week followed by 1000µg/week x 1 month followed by 1000µg/month for the rest of patient’s life (pernicious)
- Brisk reticulocytosis occurs in 5-7 days, hematological picture normalizes in 2 months; Fe may drop; Potassium may drop
- Oral Cobalamin 1000µg/day x 1 month followed by 125-500µg/day for intake deficiency and food-cobalamin malabsorption or 1000µg/day for pernicious anemia
- Endoscopic surveillance every 3-5 years with multiple biopsies even in the absence of macroscopic lesions is recommended for patients with pernicious anemia because of increased frequency of gastric neoplasms
- Treatment of underlying cause
Anaphylaxis to fresh frozen plasma in a patient with severe IgA deficiency:

1. Is unlikely
2. Is often due to contamination with latex allergen
3. Presents atypically
4. Is usually due to anti-IgA antibodies
5. None of the above

Types of IgA

- **STRUCTURE**
  2 heavy and 2 light chains
  - 2 antigen binding sites Fab
  - 1 cell-binding site Fc
  - Cysteine residues
    - Bind to alpha-1 antitrypsin, fibronectin and lactoferrin
  - Monomeric IgA (serum)
  - Secretory IgA: Dimeric with secretory piece (80 kD)
  - Breast milk
  - Mucosal tissue

- Second most abundant immunoglobulin in serum
- 2 subtypes: IgA1 and IgA2
- Half life 3-6 days only
- IgA-producing B lymphocytes are found in GI, Genitourinary and Sinopulmonary tissues

What is IgA Deficiency?

- Inability to produce antibodies of IgA1 and IgA2 subclasses
- Most common of primary antibody deficiencies
  - Incidence: 1/600
- Selective IgAD: Serum IgA level <5 mg/dL
- Partial IgAD: Serum IgA level detectable but decreased 2SD less than general population age-adjusted means

Etiology

- Familial (up to 25%)
- Most cases are sporadic
- Drugs: Phenytoin, sulfasalazine, penicillamine, valproic acid, carbamazepine, thyroxine (reversible)
- Infections: toxoplasmosis, rubella, cytomegalovirus (reversible)
- Bone marrow transplantation from IgAD donor
- Occupational exposure to benzene
Presumed Molecular Defect

Exact defect is unknown

- Sometimes familial
- Many times sporadic
- B cell differentiation defect?
- Role of anti-IgA antibody in mother?
- Role of T cell-mediated B cell suppression

Normal antibody synthesis and primary deficiencies

SIgAD, selective IgA deficiency

IgA <5mg/dL

- Normal levels of IgG and IgM (SIgA deficiency)
- Low levels of IgG2 and 4 subclasses may be seen
- We have seen associated defects in complement pathways (Mannose binding lectin)
- Some cases of IgAD may remit spontaneously
- Some patients may evolve in common variable immune deficiency (Low IgG, IgA and IgM) requiring infusions
- Anti-IgA antibodies may be present and cause anaphylaxis to blood products
- Susceptibility to respiratory infection, autoimmunity and GI tract malignancies

Autoimmunity in IgA Deficiency

- Multiple autoantibodies may be detected in absence of disease
- Connective tissue disease:
  - RA, SLE, DM, Sjogrens-like, Still’s disease
  - Vasculitis- HSP, cerebral vasculitis
- Hematological disease:
  - Pernicious anemia, transfusion reactions, Coomb’s positive hemolytic anemia, ITP
- Endocrinopathy
  - Addison’s disease
- Others:
  - Vitiligo, Diabetes mellitus, PBC, IBD

Treatment

- Treat infections promptly and effectively
- Identify and treat comorbid conditions
- Functional Endoscopic Sinus Surgery (FESS)
- Tympanostomy tubes in CSOM
- Pneumococcal and other polysaccharide vaccinations
- I.V. or S.C. IgG in patients with IgA + CVID
- Precautions should be taken while transfusing blood products to avoid anaphylaxis