Autoimmune Cytopenias

Autoimmune disease is responsible for many cases of significant anaemia and thrombocytopenia. This article presents a case-based guide to diagnosing autoimmune cytopenias, including an insight into fascinating new treatments.

Hematologists are fairly simple people. We think of blood the same way we think of money. If you don’t have enough it’s either because you aren’t making it, or because you’re spending it faster than you can make it. In the case of blood cells, this means either underproduction in the bone marrow, or destruction/loss in the peripheral blood. It is into this latter category we fit autoimmune cytopenias:

- Autoimmune Haemolytic Anaemia (AIHA),
- Immune Thrombocytopenia (ITP) and
- Autoimmune Neutropenia (AIN).

All of these disorders represent excessive destruction of normal blood cells by a misfiring immune system, and share similarities in their pathogenesis and treatment. In each disease there is a spectrum of severity, and the clinical importance is usually proportional to the severity of the cytopenia.

Autoimmune Haemolytic Anaemia (AIHA)

Case 1. A 46 year old woman presents with 4 weeks of progressive fatigue and exercise intolerance. She is jaundiced with generalised pallor and mild splenomegaly. Lab tests reveal an Hb of 72, mcv 102, WCC 9.0 and platelets 204. The film comment mentions “spherocytes and polychromasia”.

You should consider autoimmune Haemolysis whenever you are confronted by a normocytic/ mildly macrocytic anaemia. A general approach to the cause of normocytic anaemia is shown in Flow Sheet 1.

Clinical suspicion of autoimmune haemolysis may be raised if the patient is jaundiced or complains of dark urine. The onset of disease can be rapid, but is more commonly insidious, and patients may not present until they are markedly anaemic. The list of causes of normocytic anaemia is long, and a methodical approach can help to arrive quickly at a diagnosis. A suggested approach is to consider three questions and perform the appropriate tests.

Question 1: Is the patient haemolysing?

Tests: bilirubin, LDH, haptoglobin, reticulocytes, urinary haemosiderin.

The combination of a high LDH/bilirubin and low haptoglobins is very specific. Patients with healthy marrow should have increased reticulocytes in an attempt to compensate, causing a slightly raised MCV. A positive urinary haemosiderin may assist diagnosis in difficult cases.

Question 2. Is haemolysis immune or nonimmune?


A positive Coombs test indicates antibody or complement coating the red cell. This strongly suggests autoimmune haemolysis, though may also be found after blood transfusion (alloimmune), and incidentally after certain medications. If the red cells are predominantly coated with IgG, this is referred to as “warm” AIHA. Cases where complement predominates are referred to as “cold” AIHA.

Note the blood film may show characteristic changes of polychromasia (increased young red blood cells) accompanied by spherocytes (warm) or agglutination (cold), see Table 3.

Question 3. What is the specific cause?

Tests: FBC, Lupus serology, +/- flow cytometry.

Rather than wading through long lists, approach the most likely causes first. For “warm” haemolysis: these include Lupus (often with few other Lupus manifestations), CLL and drugs (e.g. penicillins). When these are excluded the diagnosis by default is usually “idiopathic” haemolysis. “Cold” AIHA may be secondary to infection, (especially mycoplasma or EBV), low grade lymphomas, or be primary when no cause is identified.

Treatment

Corticosteroids remain the backbone of treatment. Prednisone at 1mg/kg/day can produce an initial response in 2/3 of patients after 3 weeks, after which time it is gradually weaned. If a cause has been identified eg CLL, specific treatment may be helpful. Other immunosuppressants, eg cyclophosphamide may be used where there is refractory disease or steroid complications. Rituximab, an intravenous monoclonal antibody targeting CD20 positive mature B lymphocytes is not yet PBS subsidised for this indication, but anecdotal reports suggest significant benefit. Ultimately splenectomy may be required in persistent warm haemolysis, but is ineffective for most “cold” AIHA.

Treatment of cold AIHA consists of avoiding cold exposure and therapy for any identified cause (e.g. lymphoma). A course of Rituximab may again induce remission for prolonged periods.
Immune Thrombocytopenia (ITP)

**Case 2.** A 58 year old man has recently arrived in Australia from Iran, and takes no medications. For 6 weeks he has noted easy bruising on his forearms. He presents complaining of 3 days persistent minor epistaxis, blood blisters on his tongue and a petechial rash on his hands and feet. His INR/APTT are normal, but FBC reveals Hb 125, WCC 7.0 and platelets 8.

ITP is the most common autoimmune cytopenia. Here the autoantibody mediates both platelet destruction and often reduced production. Mild cases (platelets >50) may be diagnosed incidentally, while severe thrombocytopenia (<20) presents with bruising, petechiae and mucosal bleeding eg epistaxis. There are important differences between ITP observed in children and adults. In children ITP is classically postviral and self-remits in 80% of cases without treatment. In adults it is usually (80%) idiopathic and a chronic immune process.

**Diagnosis** is made by exclusion of other potential causes of moderate to severe thrombocytopenia (see Flow Sheet 2). These may include alcohol, myelodysplasia, hypersplenism, infection, thrombotic thrombocytopenia purpura (TTP), bone marrow disorders, and drugs such as quinine. An appropriate screening panel may include serology for Lupus, anticardiolipin antibodies, HIV, hepatitis and H pylori. A specific test to diagnose ITP remains elusive. The blood film appearance is typically bland apart from scanty, large platelets. Current methods of measuring antiplatelet antibodies are not sufficiently accurate for routine use. Bone marrow examination, when performed, may show normal or increased production of precursor megakaryocytes.

**Treatment**

Not all patients with ITP need treatment: the benefits should be weighed against the risks of long term immunosuppression. Patients maintaining a count greater than 30 will rarely bleed and may be closely observed without therapy.

In those needing treatment, corticosteroids are again first line, both prednisone 1mg/kg po and dexamethasone 40mg po for 4 days are effective. Non-responders may derive short lived benefit from Intravenous Gamma Globulin (IVIG). A raft of second line agents (e.g. Danazol, Dapsone) have been used, but none appear superior. Recent evidence also supports a role for Rituximab in producing prolonged remissions in this disease. ITP is a chronic disease in many adult sufferers. Splenectomy will produce response in 2/3 and may avoid the need for long term drug therapy. A small group of patients may prove refractory even to splenectomy. New hope for these sufferers exists with the recent discovery of targeted thrombopoetin (TPO) agonists currently in clinical trial, e.g. Romiplostim. TPO stimulates the production of platelets by megakaryocytes, and daily use of TPO agonists appears to sustain a normal platelet count in trials to date.

Autoimmune Neutropenia (AIN)

**Case 3.** A 14 year old girl has missed several weeks of school this year for throat and ear infections. A minor cut on her foot has taken weeks to heal and she feels “run down”. Examination is otherwise unremarkable. FBC results are HB 134, WCC 1.8 and platelets 345. The absolute neutrophil count is 0.6 with no abnormal cells seen on the blood film. Repeat testing after 1 week shows the neutrophil count to be 0.3.

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>Polychromasia</td>
<td>Increased young red cell production eg. blood loss, haemolysis, treated iron deficiency</td>
<td>Check reticulocytes, haemolysis screen</td>
</tr>
<tr>
<td>Rouleaux</td>
<td>Red cells aggregated like “a stack of coins”.</td>
<td>Check ESR and QEP</td>
</tr>
<tr>
<td>Spherocytes</td>
<td>Spherical red cells due to removal of excess membrane</td>
<td>Check for haemolysis, Coombs Test</td>
</tr>
<tr>
<td>Agglutination</td>
<td>Clumping of many red cells</td>
<td>Check for Haemolysis, Coombs Test, cold agglutination</td>
</tr>
<tr>
<td>Teardrops</td>
<td>Tear shaped red cells, seen in Vit B12 def, myelofibrosis, infiltration, thalassemia</td>
<td>Check Vit B12, Haematologist referral</td>
</tr>
<tr>
<td>Elliptocytes</td>
<td>Thin pencil shaped cells seen in iron deficiency or hereditary</td>
<td>Check iron stores</td>
</tr>
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AIN is a rare disease that usually presents in infants with recurrent infections, particularly otitis media and URTIs. Antigranulocyte antibodies are detectable in the majority of cases. The neutropenia, while often severe, tends to be self-limiting with remissions observed after 1-2 years. A syndrome of “chronic neutropenia” without any clear cause may also occur in young adults. Unfortunately these older onset cases tend to be chronic and persistent. Patients may stay remarkably free of serious infection despite neutrophil counts <0.5/nL. Therapy with regular Granulocyte Colony Stimulating Factor (GCSF) is suggested for patients with recurrent infection. Immunosuppression is generally ineffective and may increase the risk of infection.

It should be remembered that the majority of cases of neutropenia are reactive in nature, with common causes being acute infection and medication toxicity. Any patient with persistent or moderate neutropenia (<1/nL) should be referred to a Haematologist for further investigation to exclude bone marrow pathology. The importance of repeating the FBC cannot be over emphasised in any case of neutropenia or thrombocytopenia. A short lived cytopenia was probably reactive, but persistent cytopenia should prompt further investigation.

**Summary**
When dealing with significant cytopenias is it useful to consider the potential causes as underproduction (e.g. bone marrow pathology, deficiency of iron/B12) or peripheral destruction. The autoimmune cytopenias are an important cause of antibody mediated peripheral destruction of blood cells. The patient history is often unremarkable, and the GP then has to rely on simple laboratory tests to exclude alternative diagnoses, and assist referral to the Haematologist. Immune suppression remains the mainstay of therapy; however, treatment of these disorders continues to advance through the discovery and trial of exciting targeted medications.

**Dr Matthew Wright**
Haematologist
T: 9476 5222
E: mwright@clinipath.net