Erythropoietin resistant anemia and iron overload

Stump the Consultants
› Annual Dialysis Conference, Kansas City, February 8th 2020

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BC Children’s Hospital
Case Presentation

› 17-year-old indigenous male with MPO-ANCA Associated Vasculitis

› Previously healthy prior to presenting in ESRD

› Initial Creatinine of 3560μmol/L (40mg/dL) and urea 82mmol/L (29mg/dL)

› Renal Biopsy: 90% of glomeruli were globally sclerosed with fibrous crescents

› Induction therapy for MPO-AAV
  › Methylprednisolone 1 gram IV x 3 days followed by oral prednisone
  › Cyclophosphamide 750mg IV x 5 doses total
Initial Renal Replacement Therapy

› January 28th: Initiated on CRRT upon presentation

› January 30th: Transition to 4x weekly Hemodialysis while PD catheter healed

› February 28th: Discharge home on CCPD
Clinic Visit - 4 months post initiation of PD

Symptoms:
› Nausea/Vomiting
› Loss of Appetite
› Weight loss
› Muscle Weakness
› Fatigue

Physical Exam
› Weight 74.4 kg (72\textsuperscript{nd} %ile), Height 175cm (43\textsuperscript{rd} %ile)
› Blood pressure: 122/60mmHg
› Dental caries, normal gingiva
› Normal Cardiorespiratory examination
› Abdomen soft, non-tender, no organomegaly. Peritoneal catheter exit site was normal.
› No petechiae, purpura or bruising. Striae present on abdomen and flank.
› No arthritis or rashes
Medications:

- Amlodipine 15mg po daily
- Calcium Carbonate 750mg TID with meals
- Darbepoetin 50mcg sc q7days (0.67mcg/kg/wk)
- Vitamin D 1000 IU po daily
- SMX-TMP 1 tab po daily
- Replavite (renal multivitamin) 1 tab po daily
- Ranitidine 150mg po daily
- Prednisone 5mg po daily
- MMF 500mg po q12h. (250mg/m²/dose)
- Ondasetron 8mg po q8h as needed

Dietary Intake Pre-Dialysis

Supplements:
- Renal Novosource® 235ml per day

Breakfast:
- nothing

Lunch:
- 2-3 eggs
- 2 slices of white bread
- Ice tea or water

Dinner:
- Meat: steak, salmon, ribs, moose meat
- Pasta or rice
Laboratory Investigations

- Hemoglobin 74g/L
- Reticulocyte count: $52 \times 10^9$/L (0.52 %)
- MCV: 95fL
- Ferritin: 1090μg/L
- Iron: 34μmol/L
- Transferrin saturation: 108%
- iPTH 13.6pmol/L
- Bicarbonate 25mmol/L
- CRP <5 mg/L
Initial Management

- Increased dosing of darbepoetin up to 80mcg once weekly (1.1mcg/kg/week)
- MMF discontinued changed to Myfortic 360mg po q12h
- Transitioned to 4x weekly HD
  - stdKt/V 2.1
  - spKt/V 1.46

Despite improved dialysis adequacy and sequential increasing doses of ESA our patient remained severely anemic with ongoing weight loss, nausea, and muscle weakness
What is the differential diagnosis for erythropoietin resistance?
## Causes of Erythropoietin resistance in HD

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Our patient</th>
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<tbody>
<tr>
<td><strong>Nutritional</strong></td>
<td>???</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>X</td>
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<tr>
<td>• Aluminum toxicity</td>
<td></td>
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<tr>
<td>• ACEi or ARB</td>
<td></td>
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<tr>
<td><strong>Inflammation</strong></td>
<td>X</td>
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<tr>
<td>• Malignancy</td>
<td></td>
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<tr>
<td>• Chronic inflammation or infection</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic Kidney Disease Management</strong></td>
<td>X</td>
</tr>
<tr>
<td>• Secondary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>• Metabolic Acidosis</td>
<td></td>
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<tr>
<td>• Dialysis inadequacy</td>
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<tr>
<td><strong>Other</strong></td>
<td>X</td>
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<tr>
<td>• Bone marrow fibrosis</td>
<td></td>
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<tr>
<td>• Hemoglobinopathies</td>
<td></td>
</tr>
<tr>
<td>• Multiple myeloma</td>
<td></td>
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<tr>
<td>• Chronic Hemolysis</td>
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</table>

What nutritional deficiencies are hemodialysis patients at risk for?
Nutritional deficiencies associated with ESA resistance

› Iron deficiency (most common)
› Folate deficiency
› Vitamin B12 deficiency
› L-Carnitine deficiency
› Vitamin C deficiency
Laboratory Investigations

› Copper 12.7 μmol/L (10.1-18.4)
› Selenium 1.42 μmol/L (1.32-2.35)
› Zinc 10.4 μmol/L (9.8-17.9)
› Vitamin B12 785 pmol/L (>120)
› **Vitamin C 21 μmol/L (LOW)**
  › Vitamin C Deficient (<11 μmol/L or < 0.2mg/dL)
  › Vitamin C Insufficient (<24 μmol/L or <0.4mg/dL)
Question #3

What are the signs and symptoms of Vitamin C deficiency?
Vitamin C Deficiency

Symptoms
› Weakness
› Fatigue
› Malaise
› Minor Bleeding
› Myalgia & Arthralgia

Signs
› Gingival Hypertrophy
› Petechiae
› Hyperkeratosis
› Poor wound healing
› Arthritis
› Anemia
Vitamin C

- The primary source of Vitamin C is fruits and vegetables.
- CKD patients are at increased risk of vitamin C deficiency due to K⁺ restrictions limiting fruit and vegetable intake.
- Vitamin C has a low molecular weight (176.1 g/mol) and is highly water soluble, making it easily removed from the plasma during dialysis.
- Vitamin C acts as a reducing agent to increase bioavailability of iron.
  - Can be used in vitamin C deficient patients with iron-overload (>1000μg/L), with or without anemia.
Case Resolution

- Ascorbic acid 125mg po daily x 3mo then decreased to 62.5mg po daily for maintenance

- Improved appetite, less nausea, improved muscle strength and exercise tolerance

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<thead>
<tr>
<th></th>
<th>At Diagnosis</th>
<th>6 weeks later</th>
<th>12 weeks later</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>74</td>
<td>102</td>
<td>130</td>
</tr>
<tr>
<td>Absolute Reticulocyte Count</td>
<td>54 x10⁹</td>
<td>87 x10⁹</td>
<td>143 x10⁹</td>
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<tr>
<td>Ferritin (µg/L)</td>
<td>1090</td>
<td>252</td>
<td>492</td>
</tr>
<tr>
<td>Transferrin (%)</td>
<td>1.08</td>
<td>&lt;0.09</td>
<td>0.37</td>
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<tr>
<td>Vitamin C (µmol/L)</td>
<td>21</td>
<td></td>
<td>90</td>
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Response to therapy

Hemoglobin (g/L)

Initiation of Vitamin C
NKF-KDOQI guidelines

- Initiation of vitamin C supplementation and dose depends on patient’s nutritional status, dietary intake, co-morbid conditions and dialysis modality.

- Dietary and supplementary intake of Vitamin C greater than DRI for age is a risk factor for secondary oxalosis
  - Considering monitoring oxalate levels when pursuing extra vitamin C supplementation

Take Home Points

› Signs of Vitamin C deficiency can mimic symptoms of uremia
› Vitamin C deficiency is common in dialysis patients
› Dialysis patients are at increased risk of Vitamin C deficiency
› Erythropoietin resistant anemia should trigger evaluation of nutritional intake in dialysis patients, including Vitamin C
› Increased risk of secondary oxalosis in doses that exceed the DRI
References


References Continued


Orange you glad you came to ADC!

Thank you!