범혈구 감소증에 대한 접근 및 증례

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CASE 1

24/M

- 24세 남자 환자가 3개월부터 시작된 자주 앉아 불고 기분이 없는 증상을 주소로 내원하였다.
- 전력건강한 젊은 남자가 3개월 전부터 양쪽 발목부, 전체가 퉁둑 퉁둑이 들어 있음을 발견하였다. 환자는 자신이 왜 앉아있었는지 기억하지 못하였다.
- 2개월 전부터 자주 코피를 흘렸고 잘 지속되지 않았다. 알코올을 향해도 술이 되어 흉통이 났다.
- 야간에는 경련이 있었고 1시간 이상 잠을 못 주도로 잠을 했으나 최근 들어 계단 올 3층 정도 올라가면 숨이 페고 라닝어질 뿐만 아니라 정신도 어려운 상태에 비해 잘 수 없었다.

Bleeding tendency

- Thrombocytopenia
  - Petechiae (<0.3cm)
  - e.g. purpura (0.3-1cm)
  - ecchymosis (>1cm)
- Skin
- Large joint (hemarthrosis)

Coagulation system
- Bruise, hematoma
### Reading of CBC results

**Anemia vs. combined cytopenia**
- Bicytopenia
  - Anemia + Thrombocytopenia
  - Anemia + leucopenia (neutropenia)
- Thrombocytopenia + leucopenia
- Pancytopenia
  - Hb < 10 g/dL.
  - Pt < 100 x 10^3/L.
  - Neutrophil count < 1.5 x 10^3/L.

### CAUSES OF PANCYTOPENIA

**Pancytopenia with Hypocellular Bone Marrow**
- Acquired aplastic anemia
- Inherited aplastic anemia (Fanconi anemia and others)
- Some myelodysplasia syndromes
- Rare atypical leukemia (acute myelogenous leukemia)
- Some acute lymphoblastic leukemias
- Some lymphomas of bone marrow

**Hypocellular Bone Marrow ± Cytopenia**
- Q fever
- Legionnaires disease
- Mycobacteria
- Tuberculosis
- Anemia nervosa, starvation
- Hypothyroidism
Causes of pancytopenia

Pancytopenia with Cellular Bone Marrow
- Primary bone marrow diseases
- Myelodysplasia syndromes
- Paroxysmal nocturnal hemoglobinuria
- Myelofibrosis
- Some aleukemic leukemias
- Myelophthisis
- Bone marrow lymphoma
- Hairy cell leukemia
- Secondary to systemic diseases
- Systemic lupus erythematosus, Sjogren syndrome
- Hypersplenism
- Vitamin B<sub>12</sub> folate deficiency (familial defect)
- Overwhelming infection
- Alcohol
- Bronchitis
- Ehrlichiosis
- Sarcoidosis
- Tuberculosis and atypical mycobacteria

Differential diagnosis of pancytopenia

Secondary cause
- Infection
- Anemia / hypoplasia
- Rheumatic disease
- Vitamin B<sub>12</sub>/folic deficiency
- Systemic disease (splenic, surgery)
- Drug
- Anemia (related to organ failure)

Primary hematologic disease (need BM biopsy)
- Myelodysplastic syndrome
- Acute leukemia (acute)
- Lymphoma
- Uremia
- Aplastic anemia (acquired, inherited)
- PNH

Table 1. Causes of neutropenia in adults

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Post-infections, Active infection (epidemic, virulent)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Agranulocytosis, Malignant neutropenia</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Primary autoimmune, Secondary autoimmune</td>
</tr>
<tr>
<td>Fatty syndromes</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Acute leukemia, Myelodysplasia</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Leukemia, Myeloma, Myelophthisic processes</td>
</tr>
<tr>
<td>Drugs</td>
<td>D-related deficiency, Copper deficiency</td>
</tr>
<tr>
<td>Global caloric malnutrition</td>
<td></td>
</tr>
</tbody>
</table>

Case 2. 91/M

1. AGC
   - s/p radical subtotal gastrectomy (96.1)
   - s/p adi FP #6
2. Pul. Tbc (357A)
   - s/p HREZ
   - h/o Tbc pleurisy (14.7)
3. h/o RT. secondary pneumothorax
   - d/t underlying lung dz, more likely
   - s/p C-tube insertion (14.7.25)
   - s/p pneumocystis (14.6.1)
4. Bronchococcalis, Empysema
5. Hospital-acquired pneumonia (1MA)

S) Pancytopenia

Case 2. 91/M (cont.)

WBC: Hb/Hct: platelet count (ANC) MCV/MCH/MCHC RDW retic (RPI)
- [15.03.16] 4100-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8/94/94/32/4/15.8/94/33/24/15.9%
- [15.03.21] 7400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8/
- [15.03.26] 7400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.03.31] 9400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.02] 7500-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.07] 7500-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.08] 3000-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%

Medications
- Mopropen 14/500mg 2.00 W/A
- IVF 3, 1/100
- Nebudin 40mg 1.00 IV A
- NS 1, 1/100
- Pyrazinamide tab 400mg 2.00 TAB 1/100
- Yulanzaz tab 400mg 3.00 TAB 1/100
- Pyridoxine tab 40mg 1.00 TAB 1/100

: INFECTION-ASSOCIATED

Case 3. 51/M

1. Heavy alcoholics (108, 2-3/0)
2. Acute hepatitis, alcohol-associated

WBC: Hb/Hct: platelet count (ANC) MCV/MCH/MCHC RDW retic (RPI)
- [15.03.16] 4100-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8/94/32/4/15.8/94/33/24/15.9%
- [15.03.21] 7400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8/
- [15.03.26] 7400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.03.31] 9400-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.02] 7500-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.07] 7500-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%
- [15.04.08] 3000-115/3.9-14/2.55/27.1-34/2 (2210) 98/33/24/15.8%

Medications
- Mopropen 14/500mg 2.00 W/A
- IVF 3, 1/100
- Nebudin 40mg 1.00 IV A
- NS 1, 1/100
- Pyrazinamide tab 400mg 2.00 TAB 1/100
- Yulanzaz tab 400mg 3.00 TAB 1/100
- Pyridoxine tab 40mg 1.00 TAB 1/100

: INFECTION-ASSOCIATED
Case 3. 51/M (cont)

#1. Heavy alcoholics (대장 소화 2-3번)
#2. Acute hepatitis, alcohol-associated

Alcohol-associated
1) Direct bone marrow suppression
2) Cirrhosis → hypersplenism

Alcoholic liver cirrhosis with portal hypertension.
- Innumerable cirrhotic nodules with marked fatty infiltration in right hepatic lobe.
- Splenomegaly.
- Pernicious and perisplenic varicos.
  Gastrorenal shunt.

Case 4. 73/M

#1. EGC
s/p TG(56.7)

S) 최근 pancytopenia가 약 약
수일이 되어 다시의 희혈이 없어도 잘스럽지 않는
기관 희혈을 잘 슬로 잘하고 있어 자주 한다.
O) [10.10.20] 4800:12.136.9-215K 93/3133 14.9% (6.610)
VIII: 12 /10:19: 174
[14.10.4] 3500: 5.5/16.3 - 86K 11940/34 23.0% (1590)
VIII: 12 /RBC folate: 35.5 / 8.2
Iron/TIBC/serum: 216/236/169.3
A) Megaloblastic anemia + neurologic symptoms + tongue inflammation
  (Vitamin B12 deficiency)
P) - Actinamid 1000mg IM x 1week (total 8 times)
Lab results (after 6 months of actinamid replacement)
[15.4.3] 4200-13.10.9.174K 4540/1411/1(1900) 90/33/33 13.7%

Case 5. 74/F

S) Pancytopenia (refererred from GS: chronic cholelithiasis)
Drug: 담장, 비타민, 관절 약 / her: 음영나무 다린 불
최근 많이 야외로 성사를 하였음(파란 1개월전부터)
관절 약을 잘못 먹었음.
O) [08.8.20] 미백로[690-11.6.5.2-217K 5140/101 100/34/33 17.2%
[08.9.1] 미백로 3140-10.8/31.9 - 69K 4944/3 100/35/34 19.1%
[08.9.2] 4000-11.5/6.0-141K 5946/172/1 (1560) 110/35/32 19.8% 2.02%
HBsAg/AN(-)/ HCV(-)
VIII: 12 /RBC folate: 637/288 (normal)
A) Transient pancytopenia, due to
R/O drug
R/O 음영나무 / 인삼

Case 5. 74/F (cont.)

S) 음영나무: meloxicam, antiserum, 프로테스, ultracet, triamcinolone,
methotrexate, folic acid
관절염을 중단하기로 했을 때 없어졌다.
O) [08.10.17] 2100-10.3/32.2-21K 3855/525/1 (790) 10735/33 17.1%
[08.10.20] 3700-10.3/32.7-89K 444/10/1(1458) 108/35/22 17.3% 0.81%
FANA: spokked 1:169 anti-dsDNA: 5.0 / 16.7 C3/C4 97/49.6
A) Pancytopenia, df/methotrexate
Underlying rheumatoid arthritis
P) - Discontinue methotrexate
- Consult rheumatology

→ Drug – associated pancytopenia
Drugs and Chemicals causing pancytopenia

Chemicals
- Benzene
- Chlorinated hydrocarbons
- Insecticides/organophosphates

Drugs
- Chemotherapeutic agents:
  - Alkylating: busulfan, cytoxan, melphalan
  - Antimetabolite: fluorouracil, methotrexate
  - Cytotoxic antibiotics: daunorubicin, doxorubicin, mitoxantrone.
- Antiprotozoal: chlorquine, pyrimethamine
- Antiarrhythmic: quinidine, tocainide

Drugs and Chemicals causing pancytopenia (continue)

- Anticonvulsant: valproic acid, ethosuximide, phenacemide
- Antiplaque: Ticlopidine.
- Antiinflammatory: diclofenac, ibuprofen, naproxen
- Antimicrobial: dapson, pencillin, nafcillin, beta-lactam, amphotericin
- Antithyroid: methimazole, PTU, sodium thiocyanate
- Sulfanamide: antibacterial
- Diuretics: thiazide, furasemide,
- Sedative: chlormethiazepoxide, chlormepazine, lium
- Etc: atoparin, interferon, Chloramphenicol

Drugs associated with neutropenia or agranulocytosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Neutrophils</th>
<th>Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>50%</td>
<td>High</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Antivirals</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Antileukemic agents</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Antithyroid drugs</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>10%</td>
<td>Low</td>
<td>Neutrophils</td>
</tr>
</tbody>
</table>

Drug-associated pancytopenia

True potential of each drug to cause neutropenia:
- Not be accurately reflected by the incidence calculated from case reports
- Not normalized to the prescription rate of the drugs
- Systematic reviews have focused exclusively on severe cases
  (mid dose-related pancytopenia can be difficult to estimate accurately)

Most cases in outpatient setting:
- Mild / dose-related / minimal concerns
- Mild pancytopenia / effective in the purpose → continue medication
- Early severe pancytopenia → discontinue immediately

Autoimmune pancytopenia

- Associated with systemic autoimmune disease (rheumatoid arthritis, SLE)
- Autoantibodies directed at specific neutrophil / red blood cell / platelet

Frequently a benign disorder
- Manifests as mild neutropenia / anemia / thrombocytopenia
- Manifestation of the activity of the underlying disorder
- Seldom needs treatment / often respond to steroid, IV immunoglobulin
- Infectious complication tend to correlated better with the degree of immunosuppressive therapy than with the degree of neutropenia

Indication of treatment
- Neutropenia: recurrent infection (ANC<500)
- Anemia: asymptomatic
- Thrombocytopenia: easy bruising (platelet <20,000 or 30,000)

Initial triage of neutropenic adult

- Yes → Admit for antibiotics, evaluation
- Yes → Drug or disease that causes neutropenia
- Yes → Infectious disease / infection
- Yes → Other complications
- Yes → Bone marrow biopsy
- Yes → Supportive care
- Yes → Hematopoietic growth factors
- Yes → Thrombopoietic platelet growth factors
- Yes → Therapeutic plasma exchange
Acquired neutropenia
- Infection / drug / autoimmune / nutritional deficiency / hypersplenism
- Hematologic malignancy

Post-infectious neutropenia
- Viral: varicella, measles, rubella, influenza, hepatitis, EBV, HIV
- Bacterial: Brucella, rickettsia, mycobacterium
- Severe sepsis (elderly) from exhaustion of marrow granulocyte reserves

Drug & toxin
- Various drugs (including chemotherapeutic drugs)


Congenital neutropenia

Constitutional neutropenia
- Chronic neutropenia (ANC<1,000)
- No history of recurrent infection
- Mediterranean and African descent

Benign familial neutropenia
- Hereditary: genetic basis is unknown
- Not related to a particular ethnic group

Cyclic neutropenia
- Episode of self-limited neutropenia (per 2-5 weeks)
- Autosomal dominant

Severe congenital neutropenia
- Agranulocytosis + recurrent severe infection
- Begin during infancy
- Genetic abnormalities: heterogeneous syndrome
- Respond to G-CSF administration

HOW TO DISCRIMINATE SECONDARY VS. PRIMARY?

Physical examination
Lymphadenopathy
- Benign vs. malignant

Splenomegaly

Tongue

Neurologic examination

Diagnostic workup
CBC/reticulocyte count
Blood cell morphology (peripheral blood smear)

Chemistry
Viral hepatitis lab (HBV, HCV, HAV)
HIV

Rheumatic disease lab (FANA, anti-dsDNA, C3/C4)
Vitamin B12 / RBC folate or folate
Lab test for rheumatic disease

- FANA / rheumatoid factor
  - Good screening test

- Antineutrophil / antiplatelet antibody
  - Rarely helpful in diagnosing adult patients
    - High false-positivity
    - Positive predictive value does not correlate with clinical significance
    - No reliable correlation between test and response to treatment demonstrated

|PERFORM BONE MARROW BIOPSY|

To observe or to refer (or to take BM exam)?

Evidence to support secondary cause

Age / comorbidity

Severity of pancytopenia

Recent laboratory results change

Subjective symptoms

Objective abnormalities in physical examinations

⇒ If decide to observe, how frequently?

Severity & Speed of change

|Case A|
|---|---|---|
|ANC| HB| Platelet|
|1,000| 100| 100K|
|750| 80| 75K|
|500| 60| 50K|
|250| 40| 25K|

|Case B|
|---|---|---|
|ANC| HB| Platelet|
|1,000| 100| 100K|
|750| 80| 75K|
|500| 60| 50K|
|250| 40| 25K|

Case 6.

<table>
<thead>
<tr>
<th></th>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
<th>Case D</th>
<th>Case E</th>
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<tbody>
<tr>
<td>Age</td>
<td>55 year</td>
<td>80 years</td>
<td>80 years</td>
<td>80 years</td>
<td>80 years</td>
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<tr>
<td>Initial</td>
<td>ANC</td>
<td>1,100</td>
<td>1,100</td>
<td>1,600</td>
<td>1,100</td>
</tr>
<tr>
<td></td>
<td>Hb</td>
<td>11.0</td>
<td>11.0</td>
<td>14.0</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>105K</td>
<td>105K</td>
<td>170K</td>
<td>105K</td>
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<tr>
<td>Time Interval</td>
<td>12m</td>
<td>6m</td>
<td>12m</td>
<td>12m</td>
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<tr>
<td>Follow-up</td>
<td>ANC</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>1,000</td>
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<tr>
<td></td>
<td>Hb</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>10.5</td>
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<tr>
<td></td>
<td>Platelet</td>
<td>75K</td>
<td>75K</td>
<td>75K</td>
<td>83K</td>
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<tr>
<td>Probability of hematologic crisis</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Priority of BM evaluation</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
HEMATOLOGIC DISEASES PRESENTED AS PANCYTOPENIA

Case 7. 22 / M
S) Epistaxis, DCE, pale face
O) [15.4.6] 38-40: 7.8: 8K (outside lab)
   → p-RBC & platelet concentrate transfusion

A) no Acute leukemia
P) BM biopsy

Case 8. 39 / M
S) 최근 피로감, 무기력감, 체중 감소는 동반, 발생 알코올 중독
   alcohol (-) drug (-) herb (-)
O) [15.4.6] 38-40: 7.8: 8K (outside lab)
   → p-RBC & platelet concentrate transfusion

A) Pancytopenia; severe / no specific cause explaining cytopenia
P) BM Bx

Case 10. 35/M, Jaundice (2 weeks ago)
S) 내원 1개월 전 일본지역에서 전염병 발생
   내원 2주 전 jaundice 발생; toxic hepatitis 의심, 절단 없음
   내원 2주 전 bilirubin 50으로 상승, 발열 자극.

O) Liver/spleen palpable
CBC 3300-7.1-85K (ANC 700)
HBsAg/anti-HBc (+) HAV IgM (-) HCV Ab screening (-) MCV IgM / IgG (-)
ANA: 1:40, IgG / IgA / IgM: 1190 / 249.0 / 153.0 mg/dL, C3 / C4: 141.0 / 38.0 mg/dL,
Ferritin: 2458.7 / 45374 ug/dL.
BM: Cellularity 60%, blast 0%, hemophagocytosis (+)
NK cell activity: 11.0% (15.0-21.9%)
Triglyceride: 967 (<159 mg/dL)

A) HLH (idiopathic or drug, 8 of 8 diagnostic criteria)
P) Start HLH 2004 treatment
Hemophagocytic lymphohistiocytosis

**Presentation**
- Fever, cytopenia, splenomegaly, liver function abnormality
- Difficult to differentiate with infection / malignancy / hepatic failure / rheumatic disease
- Prone to delayed diagnosis, misdiagnosis, or under-diagnosis

**Treatment**
- Resistant to antibiotics, antifungal agent
- Responsive to immunosuppressant (corticosteroid, calcineurin inhibitor, etoposide – HLH2004)
- Need intensive supportive care / allogeneic HSCT for REF/REL cases

**Prognosis**
- Very poor if rapid treatment is not administered
- Cause of death: organ failure, infection, bleeding

Take home message!

- Pancytopenia의 원인으로 secondary cause를 먼저 감별해야 한다.
- Secondary cause로는 infection / alcohol / hypersplenism / vitamin B12 or folate deficiency / systemic disease / rheumatic disorder / drug / anorexia nervosa등이 있다.
- Secondary cause의 감별을 위해서 history taking / physical exam / basic lab 등을 시행하여 확인한다.
- Hematologic disease를 확인하기 위한 검수검사의 시행을 위하여도는 pancytopenia의 severity의 최저의 변동 추세, 환자의 중상 등을 고려하여 결정한다.